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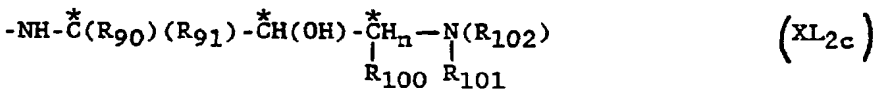

$$-NH-\overset{*}{C}(R_{90})(R_{91})-\overset{*}{C}H(OH)-\overset{*}{C}H_n-\underset{R_{100}}{\underset{|}{}}-\underset{R_{101}}{\underset{|}{N}}(R_{102}) \qquad (XL_{2c})$$

(57) Abstract

The present invention provides novel renin-inhibiting peptides of the formula $X\text{-}A_6\text{-}B_7\text{-}C_8\text{-}D_9\text{-}E_{10}\text{-}F_{11}$ containing a novel (1-amino-2-hydroxy-2-heterocyclic) ethyl moiety of the formula (XL_{2c}) at the $E_{10}\text{-}F_{11}$-position, X is a terminal group, and the remaining variables are absent or are amino acid residues. The present invention also provides novel intermediate compounds. Such inhibitors are useful for the diagnosis and control of renin-dependent hypertension and other related diseases.

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RENIN INHIBITORS CONTAINING A (1-AMINO-2-HYDROXY-2-HETEROCYCLIC) ETHYL MOIETY

BACKGROUND OF THE INVENTION

The present invention provides novel compounds. More particularly, the present invention provides novel renin-inhibiting peptide analogs and intermediates thereto. Most particularly, the present invention provides renin-inhibitory compounds having a (1-cyclohexylmethyl-1-amino-2-hydroxy-2-(2-pyrrolidinyl))ethyl end function. The renin inhibitors provided herein are useful for the diagnosis and control of renin-dependent hypertension and other related diseases.

Renin is an endopeptidase which specifically cleaves a particular peptide bond of its substrate (angiotensinogen), of which the N-terminal sequence in equine substrate is for example:

Renin
↓
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Leu-Val-Tyr-Ser- IA
1 2 3 4 5 6 7 8 9 10 11 12 13 14

as found by L.T. Skeggs et al, J. Exper. Med. 106, 439 (1957). Human renin substrate has a different sequence as recently discovered by D.A. Tewkesbury et al, Biochem. Biophys. Res. Comm. 99, 1311 (1981). It may be represented as follows:

Renin
↓
-Val-Ile-His-
11 12 13 IB

and having the sequence to the left of the arrow (↓) being as designated in formula IA above.

Renin cleaves angiotensinogen to produce angiotensin I, which is converted to the potent pressor angiotensin II. A number of angiotensin I converting enzyme inhibitors are known to be useful in the treatment of hypertension. Inhibitors of renin may also be useful in the treatment of hypertension.

A number of renin-inhibitory peptides have been disclosed. Thus, U.S. Patent 4,424,207; European published applications 45,665; 104,041; and 156,322; and U.S. patent application, Serial No. 825,250, filed 3 February 1986; disclose certain peptides with the dipeptide at the 10,11-position containing an isostere bond. A

number of statine derivatives stated to be renin inhibitors have been disclosed, see, e.g., European published applications 77,028; 81,783; 114,993; 156,319; and 156,321; and U.S. patents 4,478,826; 4,470,971; 4,479,941; and 4,485,099. Terminal disulfide cycles have also been disclosed in renin inhibiting peptides; see, e.g., U.S. patents 4,477,440 and 4,477,441. Aromatic and aliphatic amino acid residues at the 10,11 position of the renin substrate are disclosed in U.S. patents 4,478,827 and 4,455,303. Renin inhibitors containing a C-terminal amide cycle are disclosed in U.S. patent 4,485,099 and European published applications 156,320 and 156,318. Certain tetrapeptides are disclosed in European publications 111,266 and 77,027. Further, European published application No. 118,223 discloses certain renin inhibiting peptide analogs where the 10-11 peptide link is replaced by a one to four atom carbon or carbon-nitrogen link. Additionally, Holladay et al., in "Synthesis of Hydroxyethylene and Ketomethylene Dipeptide Isosteres", Tetrahedron Letters, Vol. 24, No. 41, pp. 4401-4404, 1983 disclose various intermediates in a process to prepare stereo-directed "ketomethylene" and "hydroxyethylene" dipeptide isosteric functional groups disclosed in the above noted U.S. Patent No. 4,424,207. Evans, et al., J. Org. Chem., 50, 4615 (1985) discloses the synthesis of Hydroxyethylene Dipeptide Isosteres. See also, published European patent application 163,237, which discloses certain renin inhibiting peptides.

Additionally, published European Applications 45,161 and 53,017 disclose amide derivatives useful as inhibitors of angiotensin converting enzymes.

Certain dipeptide and tripeptides are disclosed in U.S. patents 4,514,332; 4,510,085; and 4,548,926 as well as in European published applications 128,762; 152,255; and 181,110. Pepstatin derived renin inhibitors have been disclosed in U.S. patent 4,481,192. Retro-inverso bond modifications at positions 10-11 have been disclosed in U.S. patent 4,560,505 and in European published applications 127,234 and 127,235. Derivatives of isosteric bond replacements at positions 10-11 have been disclosed in European published applications 143,746 and 144,290; and U.S. patent application, Serial No. 904,149, filed 5 September 1986. Isosteric bond modifications at positions 11-12 and 12-13 have been disclosed in European published application 179,352. Certain peptides containing 2-substituted statine analogues have been

disclosed in European published application 157,409. Certain peptides containing 3-aminodeoxystatine have been disclosed in European published application 161,588. Certain peptides containing 1-amino-2-hydroxybutane derivatives at positions 10-11 have been disclosed in European published application 172,346. Certain peptides containing 1-amino-2-hydroxypropane derivatives at positions 10-11 have been disclosed in European published application 172,347. Certain peptides containing N-terminal amide cycles have been disclosed in U.S. patent application, Serial No. 844,716, filed 27 March 1986. Certain peptides containing dihalostatine have been disclosed in PCT application, Serial No. 000,713, filed 7 April 1986. Certain peptides containing C-terminus truncated epoxy or azido or cyano groups or containing a position 10-11 diol and a position 11-12 retro bond have been disclosed in U.S. patent application, Serial No. 945,340, filed 22 December 1986.

European published applications 156,322; 114,993; and 118,223; and PCT patent application, Serial No. 002,227, filed 21 November 1986; U.S. patent application, Serial No. 825,250, filed 3 February 1986; U.S. patent application, Serial No. 904,149, filed 5 September 1986; and U.S. patent application, Serial No. 844,716, filed 27 March 1986; disclose hydroxamic acids or esters at the C-terminus.

E.P. 189,203 discloses new N-dihydroxyalkyl peptide derivatives which are useful as inhibitors of renin for treating hypertension.

E.P. 184,855 discloses new hydroxy substituted-statine peptide derivatives which are useful as inhibitors of renin for treating hypertension.

Derivatives of isosteric bond replacements at positions 10-11 as dihydroxy ethylene isosteres have been disclosed in U.S. patent application, Serial No. 904,149, filed 5 September 1986.

A review of the theoretical principles of such transition-state mimetics of renin inhibitors have been recently reviewed in D.H. Rich, Chapter 5, "Inhibitors of Aspartic Proteinases," Proteinase Inhibitors, Elsevier Science Publishers BV (Biomedical Division) (1986).

The following references disclose additional substituents at the 10, 11-position: A. Spaltenstein, P. Carpino, F. Miyake and P.B. Hyskins, Tetrahedron Letters, 27:2095 (1986); D.H. Rich and M.S. Bernatowicz, J. Med. Chem., 25:791 (1982); Roger, J. Med. Chem.,

28:1062 (1985); D.M. Glick et al., Biochemistry, 21:3746 (1982); D.H. Rich, Biochemistry, 24:3165 (1985); R.L. Johnson, J. Med. Chem., 25:605 (1982); R.L. Johnson and K. Verschovor, J. Med. Chem., 26:1457 (1983); R.L. Johnson, J. Med. Chem., 27:1351 (1984); P.A. Bartlett and W.B. Kezer et al., J. Am. Chem. Soc., 106:4282 (1984); Peptides: Synthesis, Structure and Function (V.J. Hruby; D.H. Rich, eds.) Proc. 8th American Peptide Sym., Pierce Chemical Company, Rockford, Ill., pp. 511-20; 587-590 (1983).

The preparation of cyclopropyl-containing renin inhibiting peptides is disclosed in U.S. patent application, Serial No. 023,404, filed 9 March 1987, which is incorporated by reference herein.

INFORMATION DISCLOSURE

Structure-activity data have been reported on aminoalcohol isosteres of the P_1-P_1' dipeptide which contain an additional carbon atom in the P_1-P_1' linkage for stabilization of the aminal function. D.E. Ryono et al., "Potent Inhibitors of Hog and Human Renin Containing an Amino Alcohol Dipeptide Surrogate," Peptides: Structure and Function (Proceedings of the 9th Amer. Peptide Symposium, Toronto, Canada, 739-42 (1985) (Squibb); J.G. Dann et al., "Human Renin: A New Class of Inhibitors," Biochemical and Biophysical Research Communications 134:71-77 (1986) (Wellcome).

A review of the theoretical principles of transition-state mimetics of renin inhibitors have been recently reviewed in D.H. Rich, Chapter 5, "Inhibitors of Aspartic Proteinases," Proteinase Inhibitors, Elsevier Science Publishers BV (Biomedical Division) (1986).

SUMMARY OF THE INVENTION

The present invention particularly provides:

A renin inhibitory peptide having a moiety of the formula XL_{2c} corresponding to the 10,11-position of the renin substrate (angiotensinogen);

wherein * indicates an asymmetric center which is either in the R or S configuration;

wherein R_{90} and R_{91} are the same or different and are:

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het,

(e) $-(CH_2)_p-C_3-C_7$cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_{100} and R_{101} taken together with the carbon atom and the nitrogen atom to which they are bonded to form -Het;

wherein R_{102} is

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p-C_3-C_7$cycloalkyl,

(f) $R_5-O-CH_2-C(O)-$,

(g) $R_5-CH_2-O-C(O)-$,

(h) $R_5-O-C(O)-$,

(i) $R_5-(CH_2)_n-C(O)-$,

(j) $R_5-(CH_2)_n-C(S)-$,

(k) $R_4N(R_4)-(CH_2)_n-C(O)-$,

(l) $R_5-SO_2-(CH_2)_q-C(O)-$,

(m) $R_5-SO_2-(CH_2)_q-O-C(O)-$,

(n) $R_6-(CH_2)_i-C(O)-$, or

(o) $-[C(O)-AA-NH-]_jX$;

wherein aryl is phenyl or naphthyl substituted by zero to 3 of the following:

(a) C_1-C_3alkyl,

(b) hydroxy,

(c) C_1-C_3alkoxy,

(d) halo,

(e) amino,

(f) mono- or di-C_1-C_3alkylamino,

(g) -CHO,

(h) -COOH,

(i) $COOR_{26}$,

(j) $CONHR_{26}$,

(k) nitro,

(l) mercapto,

(m) C_1-C_3alkylthio,

(n) C_1-C_3alkylsulfinyl,

(o) C_1-C_3alkylsulfonyl,

(p) $-N(R_4)-C_1-C_3$alkylsulfonyl,

(q) SO_3H,

(r) SO_2NH_2,

(s) -CN, or

(t) $-CH_2NH_2$;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

(i) C_1-C_6alkyl,

(ii) hydroxy,

(iii) trifluoromethyl,

(iv) C_1-C_4alkoxy,

(v) halo,

(vi) aryl,

(vii) aryl C_1-C_4alkyl-,

(viii) amino,

(ix) mono- or di-(C_1-C_4alkyl)amino, and

(x) C_1-C_5alkanoyl;

wherein X is

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p$-C_3-C_7cycloalkyl,

(f) R_5-O-CH_2-C(O)-,

(g) R_5-CH_2-O-C(O)-,

(h) R_5-O-C(O)-,

(i) R_5-$(CH_2)_n$-C(O)-,

(j) R_5-$(CH_2)_n$-C(S)-,

(k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,

(l) R_5-SO_2-$(CH_2)_q$-C(O)-,

(m) R_5-SO_2-$(CH_2)_q$-O-C(O)- or

(n) R_6-$(CH_2)_i$-C(O)-;

wherein R_4 at each occurrence is the same or different and is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) $-(CH_2)_p$-aryl,
(d) $-(CH_2)_p$-Het,
(e) $-(CH_2)_p$-C_3-C_7 cycloalkyl, or
(f) 1- or 2-adamantyl;

wherein R_5 is
(a) C_1-C_6alkyl,
(b) C_3-C_7cycloalkyl,
(c) aryl,
(d) -Het, or
(e) 5-oxo-2-pyrrolidinyl;

wherein R_6 is
(a) hydrogen,
(b) C_1-C_5alkyl,
(c) $-(CH_2)_p$-aryl,
(d) $-(CH_2)_p$-Het,
(e) $-(CH_2)_p$-C_3-C_7cycloalkyl, or
(f) 1- or 2-adamantyl;

wherein R_{26} is
(a) hydrogen,
(b) C_1-C_3alkyl, or
(c) phenyl-C_1-C_3alkyl;

wherein i is zero to five, inclusive;

wherein j is one to three, inclusive;

wherein for each occurrence n is independently an integer of zero to five, inclusive;

wherein p is zero to two, inclusive;

wherein q is one to five, inclusive.

The present invention also provides the following novel intermediate compounds:

A peptide of the formula III

wherein X is
(a) hydrogen,
(b) C_1-C_7alkyl,
(c) $-(CH_2)_p$-aryl,
(d) $-(CH_2)_p$-Het,
(e) $-(CH_2)_p$-C_3-C_7cycloalkyl,
(f) R_5-O-CH_2-C(O)-,
(g) R_5-CH_2-O-C(O)-,

(h) R_5-O-C(O)-,
(i) R_5-$(CH_2)_n$-C(O)-,
(j) R_5-$(CH_2)_n$-C(S)-,
(k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,
(l) R_5-SO_2-$(CH_2)_q$-C(O)-,
(m) R_5-SO_2-$(CH_2)_q$-O-C(O)- or
(n) R_6-$(CH_2)_i$-C(O)-;

wherein A_6 is absent or a divalent moiety of the formula XL_1, XL_2, XL_{2a} or XL_{2b};

wherein B_7 is absent or a divalent moiety of the formula XL_b;

wherein C_8 is absent or a divalent moiety of the formula XL_1, XL_2, XL_{2a} or XL_{2b}; and

a compound of the formula XX

wherein * indicates an asymmetric center which is either in the R or S configuration;

wherein R_{200} is

(a) hydrogen,
(b) C_1-C_7alkyl,
(c) -$(CH_2)_p$-aryl,
(d) -$(CH_2)_p$-Het,
(e) -$(CH_2)_p$-C_3-C_7cycloalkyl,
(f) R_5-O-CH_2-C(O)-,
(g) R_5-CH_2-O-C(O)-,
(h) R_5-O-C(O)-,
(i) R_5-$(CH_2)_n$-C(O)-,
(j) R_5-$(CH_2)_n$-C(S)-,
(k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,
(l) R_5-SO_2-$(CH_2)_q$-C(O)-,
(m) R_5-SO_2-$(CH_2)_q$-O-C(O)-, or
(n) R_6-$(CH_2)_i$-C(O)-;

wherein R_{300} and R_{301} are the same or different and are:

(a) hydrogen,
(b) C_1-C_7alkyl,
(c) -$(CH_2)_p$-aryl,
(d) -$(CH_2)_p$-Het,
(e) -$(CH_2)_p$-C_3-C_7cycloalkyl, or
(f) 1- or 2-adamantyl;

wherein R_{400} and R_{401} taken together with the carbon atom and

the nitrogen atom to which they are bonded to form -Het;

wherein R_{402} is

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het,

(e) -$(CH_2)_p$-C_3-C_7cycloalkyl,

(f) R_5-O-CH_2-C(O)-,

(g) R_5-CH_2-O-C(O)-,

(h) R_5-O-C(O)-,

(i) R_5-$(CH_2)_n$-C(O)-,

(j) R_5-$(CH_2)_n$-C(S)-,

(k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,

(l) R_5-SO_2-$(CH_2)_q$-C(O)-,

(m) R_5-SO_2-$(CH_2)_q$-O-C(O)-,

(n) R_6-$(CH_2)_i$-C(O)-,

(o) -$[C(O)$-AA-NH-$]_j X_1$, or

(p) -C=N-C_1-C_7alkyl;

wherein aryl is phenyl or naphthyl substituted by zero to 3 of the following:

(a) C_1-C_3alkyl,

(b) hydroxy,

(c) C_1-C_3alkoxy,

(d) halo,

(e) amino,

(f) mono- or di-C_1-C_3alkylamino,

(g) -CHO,

(h) -COOH,

(i) $COOR_{26}$,

(j) $CONHR_{26}$,

(k) nitro,

(l) mercapto,

(m) C_1-C_3alkylthio,

(n) C_1-C_3alkylsulfinyl,

(o) C_1-C_3alkylsulfonyl,

(p) -$N(R_4)$-C_1-C_3alkylsulfonyl,

(q) SO_3H,

(r) SO_2NH_2,

(s) -CN, or

(t) $-CH_2NH_2$;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

(i) C_1-C_6alkyl,

(ii) hydroxy,

(iii) trifluoromethyl,

(iv) C_1-C_4alkoxy,

(v) halo,

(vi) aryl,

(vii) aryl C_1-C_4alkyl-,

(viii) amino,

(ix) mono- or di-(C_1-C_4alkyl)amino, and

(x) C_1-C_5alkanoyl;

wherein X is

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p$-C_3-C_7cycloalkyl,

(f) R_5-O-CH_2-C(O)-,

(g) R_5-CH_2-O-C(O)-,

(h) R_5-O-C(O)-,

(i) R_5-$(CH_2)_n$-C(O)-,

(j) R_5-$(CH_2)_n$-C(S)-,

(k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,

(l) R_5-SO_2-$(CH_2)_q$-C(O)-,

(m) R_5-SO_2-$(CH_2)_q$-O-C(O)- or

(n) R_6-$(CH_2)_i$-C(O)-;

wherein R_4 at each occurrence is the same or different and is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p-C_3-C_7$ cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_5 is

(a) C_1-C_6alkyl,

(b) C_3-C_7cycloalkyl,

(c) aryl,

(d) -Het, or

(e) 5-oxo-2-pyrrolidinyl;

wherein R_6 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p-C_3-C_7$cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_{26} is

(a) hydrogen,

(b) C_1-C_3alkyl, or

(c) phenyl-C_1-C_3alkyl;

wherein i is zero to five, inclusive;

wherein j is one to three, inclusive;

wherein for each occurrence n is independently an integer of zero to five, inclusive;

wherein p is zero to two, inclusive;

wherein q is one to five, inclusive.

By $-[C(O)-AA-NH-]_jX$ is meant an amino acid residue including the naturally-occurring amino acids such as: glycine, alanine, valine, leucine, isoleucine, phenylalanine, lysine, proline, tryptophan, methionine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, arginine, ornithine, and histidine, and synthetic derivatives thereof. These compounds may be in L or D configuration and are well known and readily available to those skilled in the art. In this formula, j is an integer from one to three, inclusive, so that two or three amino acid residues may be joined to yield a dipeptide or a tripeptide, respectively, and X is a terminal group.

The amino acid derivatives may be in the "D" and/or "L" configuration, the prefixes "D" and "L" being a means of indicating the

relative configurations of various optically active compounds, especially carbohydrates. The compound glyceraldehyde, $CH_2OHCHOHCHO$, was selected as a standard of reference, because it is the simplest carbohydrate - an aldotriose - capable of optical isomerism. (+)-Glyceraldehyde was arbitrarily assigned a configuration and was designated D-glyceraldehyde, and (-)-glyceraldehyde was assigned a second configuration and was designated L-glyceraldehyde. R.T. Morrison & R.N. Boyd, Organic Chemistry, 1087-88 (1978). Compounds related configuationally to D-glyceraldehyde are given the designation D, and compounds related to L-glyceraldehyde are given the designation L. Organic Chemistry at 1089.

By "renin inhibitory peptide" is meant a compound capable of inhibiting the renin enzyme in mammalian metabolism and having three or more amino acid residues linked by peptidic or pseudo-peptidic bonds.

By "a non-cleavable transition state insert" is meant a transition state insert which is not cleavable by a hydrolytic enzyme in mammalian metabolism. A variety of such transition state inserts, corresponding to the 10,11-position of the renin substrate, are known in the art, including those disclosed in the following references:

U.S. Patent 4,424,207 (Szelke); European Patent 104041A (Szelke); European Patent Application 144,290A (Ciba Geigy AG); European Patent 0,156,322 (Merck); European Patent 161-588A (Merck); European Patent 0,172,347 (Abbott); European Patent 172-346-A (Abbott); European Patent 156-318 (Merck); European Patent 157-409 (Merck); European Patent 152-255 (Sankyo); and U.S. Patent 4,548,926 (Sankyo); and

U.S. patent application, Serial No. 904,149, filed 5 September 1986; U.S. patent application, Serial No. 844,716, filed 27 March 1986; PCT application, Serial No. 000,713, filed 7 April 1986; U.S. patent application, Serial No. 945,340, filed 22 December 1986; and U.S. patent application, Serial No. 825,250, filed 3 February 1986; and

A. Spaltenstein, P. Carpino, F. Miyake and P.B. Hyskins, Tetrahedron Letters, 27:2095 (1986); D.H. Rich and M.S. Bernatowicz, J. Med. Chem., 25:791 (1982); Roger, J. Med. Chem., 28:1062 (1985); D.M. Glick et al., Biochemistry, 21:3746 (1982); D.H. Rich, Biochemistry, 24:3165 (1985); R.L. Johnson, J. Med. Chem., 25:605 (1982); R.L.

Johnson and K. Verschovor, J. Med. Chem., 26:1457 (1983); R.L. Johnson, J. Med. Chem., 27:1351 (1984); P.A. Bartlett et al., J. Am. Chem. Soc., 106:4282 (1984); and Peptides: Synthesis, Structure and Function (V.J. Hruby; D.H. Rich, eds.) Proc. 8th American Peptide Sym., Pierce Chemical Company, Rockford, Ill., pp. 511-20; 587-590 (1983).

As is apparent to those of ordinary skill in the art, the renin inhibitory peptides of the present invention can occur in several isomeric forms, depending on the configuration around the asymmetric carbon atoms. All such isomeric forms are included within the scope of the present invention. The E isomer of the cyclopropyl amino acid is preferred. Preferably, the stereochemistry of the other amino acids corresponds to that of the naturally-occurring amino acids.

Renin inhibitory peptides commonly have protecting groups at the N-terminus and the C-terminus. These protecting groups are known in the polypeptide art. Examples of these protecting groups are given below. Any of these protecting groups are suitable for the renin inhibitory peptides of the present invention.

Preferably, the moiety of the formula XL_{2c} of the present invention may occur at the C-terminus of the renin inhibitory peptide and, as such, will, when coupled with a suitable protecting group, assume the ending position.

These compounds are shown in relation to the human renin substrate as follows:

	6	7	8	9	10	11	12	13	
	-His	Pro	Phe	His	Leu	Val	Ile	His-	
X	A_6	B_7	C_8	D_9	E_{10}	F_{11}	G_{12}	H_{13}	I_{14}	Z,

The present invention provides peptide inhibitors of renin which contain the moiety of the formula XL_{2c}.

Examples of pharmaceutically acceptable acid addition salts include: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate,

succinate, tartrate, thiocyanate, tosylate, and undecanoate.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix (C_i-C_j) indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus (C_1-C_4)alkyl refers to alkyl of one to 4 carbon atoms, inclusive, or methyl, ethyl, propyl, butyl, and isomeric forms thereof. C_4-C_7cyclic amino indicates a monocyclic group containing one nitrogen and 4 to 7 carbon atoms.

Examples of (C_3-C_{10})cycloalkyl which include alkyl-substituted cycloalkyl containing a total of up to 10 total carbon atoms, are cyclopropyl, 2-methylcyclopropyl, 2,2-dimethylcyclopropyl, 2,3-diethylcyclopropyl, 2-butylcyclopropyl, cyclobutyl, 2-methylcyclobutyl, 3-propylcyclobutyl, cyclopentyl, 2,2-dimethylcyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and isomeric forms thereof.

Examples of aryl include phenyl, naphthyl, (o-, m-, p-)tolyl, (o-, m-, p-)ethylphenyl, 2-ethyl-tolyl, 4-ethyl-o-tolyl, 5-ethyl-m-tolyl, (o-, m-, or p-)propylphenyl, 2-propyl-(o-, m-, or p-)tolyl, 4-isopropyl-2,6-xylyl, 3-propyl-4-ethylphenyl, (2,3,4- 2,3,6-, or 2,4,5-)-trimethylphenyl, (o-, m-, or p-)fluorophenyl, (o-, m-, or p-trifluoromethyl)phenyl, 4-fluoro-2,5-xylyl, (2,4-, 2,5-, 2,6-, 3,4-, or 3,5-)difluorophenyl, (o-, m-, or p-)chlorophenyl, 2-chloro-p-tolyl, (3-, 4-, 5- or 6-)chloro-o-tolyl, 4-chloro-2-propylphenyl, 2-isopropyl-4-chlorophenyl, 4-chloro-3-fluorophenyl, (3- or 4-)chloro-2-fluorophenyl, (o-, m-, or p-)trifluoro-methylphenyl, (o-, m-, or p-)ethoxyphenyl, (4- or 5-)chloro-2-methoxy-phenyl, and 2,4-dichloro-(5- or 6-)methylphenyl, and the like.

Examples of -Het include: 2-, 3-, or 4-pyridyl, imidazolyl, indolyl, N^{in}-formyl-indolyl, N^{in}-C_1-C_5alkyl-C(0)-indolyl, [1,2,4]-triazolyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-thienyl, piperidinyl, pyrryl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, pyrazinyl, piperazinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, and benzothienyl. Each of these moieties may be substituted as noted above.

As would be generally recognized by those skilled in the art of organic chemistry, a heterocycle as defined herein for -Het would not be bonded through oxygen or sulfur or through nitrogen which is within a ring and part of a double bond.

Halo is halogen (fluoro, chloro, bromo, or iodo) or trifluoromethyl.

Examples of pharmaceutically acceptable cations include: pharmacologically acceptable metal cations, ammonium, amine cations, or quaternary ammonium cations. Especially preferred metal cations are those derived from the alkali metals, e.g., lithium, sodium, and potassium, and from the alkaline earth metals, e.g., magnesium and calcium, although cationic forms of other metals, e.g., aluminum, zinc, and iron are also within the scope of this invention. Pharmacologically acceptable amine cations are those derived from primary, secondary, or tertiary amines.

The novel peptides herein contain both natural and synthetic amino acid residues. These residues are depicted using standard amino acid abbreviations (see, e.g., Eur. J. Biochem., 138, 9 (1984)) unless otherwise indicated.

In addition to the treatment of warm-blooded animals such as mice, rats, horses, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

The renin inhibitors of this invention are useful for treating any medical condition for which it is beneficial to reduce the levels of active circulating renin. Examples of such conditions include renin-associated hypertension and hyperaldosteronism, hypertension, hypertension under treatment with another antihypertensive and/or a diuretic agent, congestive heart failure, angina, and post-myocardial infarction. The renin-angiotension system may play a role in maintenance of intracellular homeostasis: see Clinical and Experimental Hypertension, 86, 1739-1742 (1984) at page 1740 under Discussion. The compounds will also be useful as molecular probes for the diagnosis and study of the physiology of blood pressure regulation or other physiological functions.

Further, the renin inhibitors of this invention may be useful in the treatment of cerebrovascular disorders and disorders of intracellular homeotasis. The possible role of the renin-angiotensin system in the maintenance of intracellular homeostasis is disclosed in

Clinical and Experimental Hypertension, 86:1739-1742 (1984). Additionally, the renin inhibitors of this invention potentiate the antithrombotic activity of a thromboxane antagonist (U.S. patent 4,558,037). The antihypertensive effect of the renin inhibitors of this invention are potentiated by combination with a thromboxane synthetase inhibitor.

The compounds of the present invention are preferably orally administered to humans to effect renin inhibition for the purpose of favorably affecting blood pressure. For this purpose, the compounds are administered from 0.1 mg to 1000 mg per kg per dose, administered from 1 to 4 times daily. The compounds of the present invention are preferably orally administered in the form of pharmacologically acceptable acid addition salts. Preferred pharmacologically acceptable salts for oral administration include the citrate and aspartate salts, although any pharmacologically acceptable salt is useful in this invention, including those listed above. These salts may be in hydrated or solvated form.

Other routes of administration include parenteral, by inhalation spray, or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example as a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectibles.

Equivalent dosages for such other routes of administration are

thus employed. The exact dose depends on the age, weight, and condition of the patient and on the frequency and route of administration. Such variations are within the skill of the practitioner or can readily be determined.

The compounds of the present invention may be in the form of pharmaceutically acceptable salts both those which can be produced from the free bases by methods well known in the art and those with which acids have pharmacologically acceptable conjugate bases.

Conventional forms and means for administering renin-inhibiting compounds may be employed and are described, e.g., in U.S. Patent No. 4,424,207 which is incorporated by reference herein. Likewise, the amounts disclosed in the U.S. Patent No. 4,424,207 are examples applicable to the compounds of the present invention.

The renin-inhibiting compounds of this invention may be administered in combination with other agents used in antihypertensive therapy such as diuretics, α and/or β-adrenergic blocking agents, CNS-acting agents, adrenergic neuron blocking agents, vasodilators, angiotensin I converting enzyme inhibitors, and the like as described, for example, in published European patent application 156 318.

For example, the compounds of this invention can be given in combination with such compounds or salts or other derivative forms thereof as:

Diuretics: acetazolamide; amiloride; bendroflumethiazide; benzthiazide; bumetanide; chlorothiazide; chlorthalidone; cyclothiazide; ethacrynic acid; furosemide; hydrochlorothiazide; hydroflumethiazide; indacrinone (racemic mixture, or as either the (+) or (-) enantiomer alone, or a manipulated ratio, e.g., 9:1 of said enantiomers, respectively); metolazone; methyclothiazide; muzolimine; polythiazide; quinethazone; sodium ethacrynate; sodium nitroprusside; spironolactone; ticrynaten; trimaterene; trichlormethiazide;

α-Adrenergic Blocking Agents: dibenamine; phentolamine; phenoxybenzamine; prazosin; tolazoline;

β-Adrenergic Blocking Agents: atenolol; metoprolol; nadolol; propranolol; timolol;
((±)-2-[3-(tert-butylamino)-2-hydroxypropoxy]-2-furananilide) (ancarolol);
(2-acetyl-7-(2-hydroxy-3-isopropylaminopropoxy)benzofuran HCl)(befun-

ololol);
((±)-1-(isopropylamino)-3-(p-(2-cyclopropylmethoxyethyl)-phenoxy)-2-propranol HCl) (betaxolol);
(1-[(3,4-dimethoxyphenethyl)amino]-3-(m-tolyloxy)-2-propanol HCl)(bevantolol);
(((±)-1-(4-((2-isopropoxyethoxy)methyl)phenoxy)-3-isopropylamino-2-propanol)fumarate) (bisoprolol);
(4-(2-hydroxy-3-[4-(phenoxymethyl)-piperidino]-propoxy)-indole);
(carbazolyl-4-oxy-5,2-(2-methoxyphenoxy)-ethylamino-2-propanol);
(1-((1,1-dimethylethyl)amino)-3-((2-methyl 'H-indol-4-yl)oxy)-2-propanol benzoate) (bopindolol);
(1-(2-exobicyclo[2.2.1]-hept-2-ylphenoxy)-3-[(1-methylethyl)-amino]-2-propanol HCl) (bornaprolol);
(o-[2-hydroxy-3-[(2-indol-3-yl-1,1-dimethylethyl)-amino]propoxy]benzonitrile HCl) (bucindolol);
(α-[(tert.butylamino)methyl]-7-ethyl-2-benzofuranmethanol) (bufuralol);
(3-[3-acetyl-4-[3-(tert.butylamino)-2-hydroxypropyl]-phenyl]-1,1-diethylurea HCl) (celiprolol);
((±)-2-[2-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]phenoxy]-N-methylacetamide HCl) (cetamolol);
(2-benzimidazolyl-phenyl(2-isopropylaminopropanol));
((±)-3'-acetyl-4'-(2-hydroxy-3-isopropylaminopropoxy)-acetanilide HCl) (diacetolol);
(methyl-4-[2-hydroxy-3-[(1-methylethyl)aminopropoxyl]]-benzenepropanoate HCl) (esmolol);
(erythro-DL-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol);
(1-(tert.butylamino)-3-[O-(2-propynyloxy)phenoxy]-2-propanol (pargolol);
(1-(tert.butylamino)-3-[o-(6-hydrazino-3-pyridazinyl)phenoxy]-2-propanol diHCl) (prizidilol);
((-)-2-hydroxy-5-[(R)-1-hydroxy-2-[(R)-(1-methyl-3-phenylpropyl)-amino]ethyl]benzamide);
(4-hydroxy-9-[2-hydroxy-3-(isopropylamino)-propoxy]-7-methyl-5H-furo[3,2-g][1]-benzopyran-5-one) (iprocrolol);
((-)-5-(tert.butylamino)-2-hydroxypropoxy]-3,4-dihydro-1-(2H)-naphthalenone HCl) (levobunolol);
(4-(2-hydroxy-3-isopropylamino-propoxy)-1,2-benzisothiazole HCl);

(4-[3-(tert.butylamino)-2-hydroxypropoxy]-N-methylisocarbostyril HCl);
((±)-N-2-[4-(2-hydroxy-3-isopropylaminopropoxy)phenyl]ethyl-N'-isopropylurea) (pafenolol);
(3-[[(2-trifluoroacetamido)ethyl]amino]-1-phenoxypropan-2-ol);
(N-(3-(o-chlorophenoxy)-2-hydroxypropyl)-N'-(4'-chloro-2,3-dihydro-3-oxo-5-pyridazinyl)ethylenediamine);
((±)-N-[3-acetyl-4-[2-hydroxy-3-[(1-methylethyl)amino]propoxyphenyl]-butanamide) (acebutolol);
((±)-4'-[3-(tert-butylamino)-2-hydroxypropoxy]spiro[cyclohexane-1,2'-indan]-1'-one) (spirendolol);
(7-[3-[[2-hydroxy-3-[(2-methylindol-4-yl)oxylpropyl]amino]butyl]thiophylline) (teoprolol);
((±)-1-tert.butylamino-3-(thiochroman-8-yloxy)-2-propanol) (tertatolol);
((±)-1-tert.butylamino-3-(2,3-xylyloxy)-2-propanol HCl) (xibenolol);
(8-[3-(tert.butylamino)-2-hydroxypropoxy]-5-methylcoumarin) (bucumolol);
(2-(3-(tert.butylamino)-2-hydroxy-propoxy)benzonitrile HCl) (bunitrolol);
((±)-2'-[3-(tert-butylamino)-2-hydroxypropoxy-5'-fluorobutyrophenone) (butofilolol);
(1-(carbazol-4-yloxy)-3-(isopropylamino)-2-propanol) (carazolol);
(5-(3-tert.butylamino-2-hydroxy)propoxy-3,4-dihydrocarbotyril HCl) (carteolol);
(1-(tert.butylamino)-3-(2,5-dichlorophenoxy)-2-propanol) (cloranolol);
(1-(inden-4(or 7)-yloxy)-3-(isopropylamino)-2-propanol HCl) (indenolol);
(1-isopropylamino-3-[(2-methylindol-4-yl)oxy]-2-propanol) (mepindolol);
(1-(4-acetoxy-2,3,5-trimethylphenoxy)-3-isopropylaminopropan-2-ol) (metipranolol);
(1-(isopropylamino)-3-(o-methoxyphenoxy)-3-[(1-methylethyl)amino]-2-propanol) (moprolol);
((1-tert.butylamino)-3-[(5,6,7,8-tetrahydro-cis-6,7-dihydroxy-1-naphthyl)oxy]-2-propanol) (nadolol);
((S)-1-(2-cyclopentylphenoxy)-3-[(1,1-dimethylethyl)amino]-2-propanol

sulfate (2:1)) (penbutolol);
(4'-[1-hydroxy-2-(amino)ethyl]methanesulfonanilide) (sotalol);
(2-methyl-3-[4-(2-hydroxy-3-tert.butylaminopropoxy)phenyl]-7-methoxy-isoquinolin-1-(2H)-one);
(1-(4-(2-(4-fluorophenyloxy)ethoxy)phenoxy)-3-isopropylamino-2-propanol HCl);
((-)-p-[3-[(3,4-dimethoxyphenethyl)amino]-2-hydroxypropoxy]-β-methyl-cinnamonitrile) (pacrinolol);
((±)-2-(3'-tert.butylamino-2'-hydroxypropylthio)-4-(5'-carbamoyl-2'-thienyl)thiazole HCl) (arotinolol);
((±)-1-[p-[2-(cyclopropylmethoxy)ethoxy]phenoxy]-3-(isopropylamino)-2-propanol) (cicloprolol);
((±)-1-[(3-chloro-2-methylindol-4-yl)oxy]-3-[(2-phenoxyethyl)amino]-2-propanol) (indopanolol);
((±)-6-[[2-[[3-(p-butoxyphenoxy)-2-hydroxypropyl]amino]ethyl]amino]-1,3-dimethyluracil) (pirepolol);
(4-(cyclohexylamino)-1-(1-naphtholenyloxy)-2-butanol);
(1-phenyl-3-[2-[3-(2-cyanophenoxy)-2-hydroxypropyl]aminoethyl]hydantoin HCl);
(3,4-dihydro-8-(2-hydroxy-3-isopropylaminopropoxy)-3-nitroxy-2H-1-benzopyran) (nipradolol);

Angiotensin I Converting Enzyme Inhibitors:

1-(3-mercapto-2-methyl-1-oxopropyl)-L-proline (captopril);
(1-(4-ethoxycarbonyl-2,4(R,R)-dimethylbutanoyl)indoline-2(S)-carboxylic acid);
(2-[2-[(1-(ethoxycarbonyl)-3-phenyl-propyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid);
((S)-1-[2-[(1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-1H-indole-2-carboxylic acid HCl);
(N-cyclopentyl-N-(3-(2,2-dimethyl-1-oxopropyl)thiol-2-methyl-1-oxopropyl)glycine) (pivalopril);
((2R,4R)-2-(2-hydroxyphenyl)-3-(3-mercaptopropionyl)-4-thiazolidinecarboxylic acid);
(1-(N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-(S)-alanyl)-cis,syn-octahydroindol-2(S)-carboxylic acid HCl);
((-)-(S)-1-[(S)-3-mercapto-2-methyl-1-oxopropyl]indoline-2-carboxylic acid);
([1(S),4S]-1-[3-(benzoylthio)-2-methyl-1-oxopropyl]-4-phenylthio-L-

proline;
(3-([1-ethoxycarbonyl-3-phenyl-(1S)-propyl]amino)-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1-acetic acid HCl);
(N-(2-benzyl-3-mercaptopropanoyl)-S-ethyl-L-cysteine) and the S-methyl analogue;
(N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline maleate) (enalapril);
N-[1-(S)-carboxy-3-phenylpropyl]-L-alanyl-1-proline;
N^2-[1-(S)-carboxy-3-phenylpropyl]-L-lysyl-L-proline (lysinopril);

Other Antihypertensive Agents: aminophylline; cryptenamine acetates and tannates; deserpidine; meremethoxylline procaine; pargyline; tri-methaphan camsylate; and the like, as well as admixtures and combinations thereof.

Typically, the individual daily dosages for these combinations can range from about one-fifth of the minimally recommended clinical dosages to the maximum recommended levels for the entities when they are given singly. Coadministration is most readily accomplished by combining the active ingredients into a suitable unit dosage form containing the proper dosages of each. Other methods of coadministration are, of course, possible.

The compounds of the present invention are prepared as depicted in the charts and as described more fully in the Preparations and Examples. In the charts, Boc represents butyloxycarbonyl; Cbz represents benzyloxycarbonyl; Ph represents phenyl.

Chart A

The synthesis of the compounds of formula A-3 and A-4 is shown in Chart A. Addition of the aldehyde of formula A-1, preparation of which is known in the art, to a twofold excess of the lithiated pyrrolidine formamide of formula A-2, prepared as described in A.I. Meyers et al., J. Amer. Chem. Soc., 106:3270-3276 (1984), in tetrahydrofuran at -80°C affords a mixture of two diastereomeric alcohols of formula A-3 and A-4. While inspection of the crude reaction by NMR clearly indicates a preference for the formation of the threo diastereomer, the alcohol of formula A-3 (2/1), purification (silica gel) always affords an approximate 1/1 mixture of the diastereomeric alcohols. The alcohol of formula A-3 is a viscous oil while the alcohol of formula A-4 is a crystalline solid. The alcohols of formula A-3 and A-4 are used as the starting materials for the

compounds prepared in Charts B and C.

CHART B

The synthesis of the compound of formula B-7 is shown in Chart B. The compound of formula A-3, prepared as described in Chart A, is used as the formula B-1 starting material. Treatment of the compound of formula B-1 with hydrazine in acidic aqueous ethanol as described by Meyers et al., J. Am. Chem. Soc. (1984) 106, 3270-76, affords the desired Boc-amino alcohol of formula B-2 as a white solid. The Boc-amino alcohol of formula B-2 is then converted to the Boc-Cbz alcohol of formula B-3. Treatment of the Boc-Cbz alcohol of formula B-3 with trifluoroacetic acid/methylene chloride (0°C) then affords the amino alcohol of formula B-4 which is coupled to histidine. Addition of triethylamine (TEA) to a mixture of Boc-L-His(πBom)-OH, the amino alcohol of formula B-4, and diethylphosphorylcyanide (DEPC) in dimethylformamide (DMF) affords the desired pseudo dipeptide of formula B-5. Since racemization may occur at either the oxidation step (alcohol to aldehyde) and/or the addition of the lithiated pyrrolidine formamide of formula A-2 to the aldehyde of formula A-1 (see Chart A), the dipeptide of formula B-5 is an approximate 2:1 mixture of diastereomers (ll and dl). The dipeptide of formula B-5 is then debocylated with 50% trifluoroacetic acid (TFA)/methylene chloride at 0°C. The resulting amine is coupled to Ac-Trp[N^{in}-For]-Pro-Phe-OH using diethylphosphorylcyanide (DEPC) as the coupling reagent to yield the compound of formula B-6 as crude material. The compound of formula B-6 is then treated with anhydrous hydrogen fluoride to remove the benzyloxycarbonyl (Cbz) and the benzoyoxymethyl protecting groups to afford, after purification, the desired peptide of formula B-7 as the trifluoroacetate (TFA) salt.

CHART C

The synthesis of the diastereomeric compounds of formula C-7 and C-8 is shown in Chart C. The compound of formula A-4, prepared as described in Chart A, is used as the formula C-1 starting material. Treatment of the compound of formula C-1 with hydrazine in acidic aqueous ethanol as described by Meyers et al., J. Am. Chem. Soc. (1984) 106, 3270-76, affords the desired Boc-amino alcohol of formula C-2. The Boc-amino alcohol of formula C-2 is then converted to the Boc-Cbz alcohol of formula C-3. Treatment of the Boc-Cbz alcohol of formula C-3 with trifluoroacetic acid/methylene chloride then affords

the amino alcohol of formula C-4. Addition of triethylamine (TEA) to a mixture of Boc-L-His(πBom)-OH, the amino alcohol of formula C-4, and diethylphosphorylcyanide (DEPC) in dimethylformamide (DMF) affords the desired pseudo dipeptide of formula C-5. As in the case of the dipeptide of formula B-5, the dipeptide of formula C-5 is also an approximate 2:1 mixture of diastereomers (ll and dl). The dipeptide of formula C-5 is then debocylated with trifluoroacetic acid (TFA)/methylene chloride (0°C), and coupled to Ac-Trp[N^{in}-For]-Pro-Phe-OH using diethylphosphorylcyanide (DEPC) as the coupling agent to yield the compound of formula C-6 as crude material. The compound of formula C-6 is then treated with anhydrous hydrogen fluoride to remove the benzyloxycarbonyl (Cbz) and the benzyloxymethyl protecting groups to afford, after purification, two diastereomeric peptides of formula C-7 and C-8.

Other renin inhibitory peptides of the present invention, which contain a moiety of the formula XL_{2c} wherein R_{90}, R_{91}, R_{100}, R_{101} and R_{102} are as defined above, may be prepared by processes analogous to those described in Charts A, B and C by using the appropriate starting materials.

Aldehydes of the formula V bearing the desired R_{90} and R_{91} groups may be obtained from the corresponding natural and unnatural protected amino acids and esters by procedures known in the art.

Lithiated heterocyclic compounds of the formula VI, wherein n is 0 or 1 to form aromatic, unsaturated and saturated compounds, wherein R_{100} and R_{101} taken together with the carbon and nitrogen atoms to which they are bonded to form the desired heterocyclic ring and wherein R_{102} is a cleavable protecting group, may be prepared by processes analogous to those described in P. Beak, Chem. Review, 84:471-523 (1984); and Handbook of Heterocyclic Compounds, Ed. A.R. Katritzky, Pergamon Press, Oxford (1985), p. 261. Such protecting groups include carbamates, aryl or alkyl amides, thioamides, ureas and formamidine. Formamidine is the preferred protecting group. When there is one heteroatom in the heterocyclic ring, lithiation occurs on the carbon atom of the ring adjacent to the heteroatom. When there is more than one heteroatom in the heterocyclic ring, lithiation occurs at the carbon atom of the ring adjacent to the heteroatom which has been activated for metallation. See, for example, P. Beak, Chem. Review, 84:471-523 (1984); A.I. Meyers et

al., J. Amer. Chem. Soc., 106:3270-3276 (1984).

Taking the appropriate aldehyde and heterocyclic compounds as starting materials and using the procedures described in Charts A, B and C, other renin inhibitory peptides of the present invention may be prepared.

Generally, the renin inhibiting polypeptides may be prepared by either polymer assisted or solution phase peptide synthetic procedures analogous to those described hereinafter or to those methods known in the art. For example, the carboxylic moiety of N^{α}-t-butyloxycarbonyl (Boc)-substituted amino acid derivatives having suitable side chain protecting groups, if necessary, may be condensed with the amino functionality of a suitably protected amino acid, peptide or polymer-bound peptide using a conventional coupling protocol such as dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) or diethylphosphoryl cyanide (DEPC) and triethylamine (Et_3N) in methylene chloride or dimethylformamide. The synthetic procedures used to incorporate the novel moieties herein are analgous to those described, for example, in U.S. patents 4,424,207; 4,470,971; 4,477,440; 4,477,441; 4,478,826; 4,478,827; 4,479,941; and 4,485,099, and copending application Serial No. 753,198, filed 9 July 1985, and copending application Serial No. 825,250, filed 3 February 1986, all of which are expressly incorporated by reference herein. See, also, published European patent applications 45,161; 45,665; 53,017; 77,028; 77,029; 81,783; 104,041; 111,266; 114,993; and 118,223.

Following coupling reaction completion, the N^{α}-Boc moiety may be selectively removed with 45% trifluoroacetic acid with or without 2% anisole (v/v) in methylene chloride. Neutralization of the resultant trifluoroacetate salt may be accomplished with 10% diisopropylethylamine or sodium bicarbonate in methylene chloride. In the case of polymer-assisted peptide synthesis, this stepwise, coupling strategy may be partially or completely automated to provide the desired peptide-polymer intermediates. Anhydrous hydrofluoric acid treatment of the peptide-polymer intermediate may then be used to effect simultaneous protecting group removal and cleavage of the peptide from its polymeric support. A notable exception to this includes N^{in}-formyl-indolyl-substituted peptides in which the N^{in}-formyl-indolyl (FTrp) moiety is stable to TFA or HF but may be removed by NH_3 or NaOH. Because FTrp is somewhat unstable to base in synthetic procedures,

possibly causing lower yields, it may be desirable in solution phase synthesis to introduce the FTrp-containing moiety late in the synthetic sequence so that it is not exposed to such conditions.

The incorporation of N^{in}-formyl-Trp into compounds of the present invention is easily accomplished because of the commercial availability of N^{α}-Boc-N^{in}-formyl-Trp-OH. However, the N^{in}-formyl moiety may be introduced into indolyl-substituted amino acid derivatives or related compounds by reaction with HCl-formic acid as reported in the literature, see A. Previero et al, Biochim. Biophys.-Acta 147, 453 (1967); Y.C.S. Yang et al, Int. J. Peptide Protein Res. 15, 130 (1980).

The novel renin inhibitory tripeptide of the formula III may be prepared by the procedures described above.

Generally, methods of alkylation useful in alkylating histidine for use in the present invention are found in Cheung, S.T. et al, Can. J. Chem., Vol 55, pp. 906-910 (1977). However it is now found that in Cheung, S. T. et al, methods it is critical that the reaction conditions for the alkylation of histidine be anhydrous. Further, it is now found also that during work-up instead of adding water directly to the reaction mixture, it is preferred that a buffered aqueous solution be added to the reaction mixture, for example, aqueous sodium or potassium hydrogen sulfate.

Variations in the above description for starting materials, reactants, reaction conditions and required protecting groups to obtain other such N-alkylated compounds are known to an ordinarily skilled chemist or are readily available in the literature.

These peptides may also be prepared by the standard solid phase techniques of Merrifield. Appropriate protecting groups, reagents, and solvents for both the solution and solid phase methods can be found in "The Peptides: Analysis, Synthesis, and Biology," Vols. 1-5, eds. E. Gross and T. Meienhofer, Academic Press, NY, 1979-1983.

The compounds of the present invention may be in either free form or in protected form at one or more of the remaining (not previously protected) peptide, carboxyl, amino, hydroxy, or other reactive groups. The protecting groups may be any of those known in the polypeptide art. Examples of nitrogen and oxygen protection groups are set forth in T.W. Greene, Protecting Groups in Organic

Synthesis, Wiley, New York, (1981); J.F.W. McOmie, ed. Protective Groups in Organic Chemistry, Plenum Press (1973); and J. Fuhrhop and G. Benzlin, Organic Synthesis, Verlag Chemie (1983). Included among the nitrogen protective groups are t-butoxycarbonyl (Boc), benzyloxycarbonyl, acetyl, allyl, phthalyl, benzyl, benzoyl, trityl and the like.

The following compounds of the present invention are preferred: N-Acetyl-1-formyl-L-tryptophyl-1-prolyl-L-phenylalanyl-N-[1-(cyclohexylmethyl)-2-hydroxy-2-(2-pyrrolidinyl)ethyl)-L-histidinamide,[R-R*,S*)]bis(trifluoroacetate) (salt); N-Acetyl-1-formyl-L-tryptophyl-1-prolyl-L-phenylalanyl-N-[1-(cyclohexylmethyl)-2-hydroxy-2-(2-pyrrolidinyl)ethyl]-L-histidinamide-[2S-[2R*(1R*,2S*)]]-bis(trifluoroacetate) (salt); and N-Acetyl-1-formyl-L-tryptophyl-1-prolyl-L-phenylalanyl-N-[1-(cyclohexylmethyl)-2-hydroxy-2-(2-pyrrolidinyl)-ethyl]-histidinamide-[2R-[2R*(1R*,2R*)]]-bis(trifluoroacetate) (salt).

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following Preparations and Examples illustrate the present invention.

In the Preparations and Examples below and throughout this document:

Ac is acetyl;
AMP is 2-(aminomethyl)pyridinyl;
BOC is t-butoxycarbonyl;
BOM is benzyloxymethyl;
Bz is benzyl;
C is centigrade;
Celite is a filter aid;
DCC is dicyclohexylcarbodiimide;
DMF is dimethylformamide;
EtOAc is ethyl acetate;
FTrp is N^{in}-formyl-indolyl;
g is grams;
GEA is 2-(quanidylethyl)amino;
GMPMA is (3-(guanidylmethyl)phenyl)methylamino;
HPLC is high performance liquid chromatography;
I_2 is iodine;
Ile is isoleucine;

IR is infra red spectra;
LVA is LeuΨ[CH(OH)CH_2]Val;
M or mol is mole;
MBA is 2-methylbutylamino (racemic or optically active);
MBAS is 2S-methylbutylamino;
Me is methyl;
min is minute;
ml is milliliter;
MS is mass spectroscopy;
NMHis is Nα-methyl-L-histidine;
NMR is nuclear magnetic resonance;
NOAl is (1-naphthyloxy)acetyl;
p-TSA salt is para-toluene sulfonic acid salt;
Ph is phenyl;
Phe is phenylalanine;
POA is phenoxyacetyl;
RIP means a compound having the formula H-Pro-His-Phe-His-Phe-Phe-Val-Tyr-Lys-OH.2($CH_3C(O)OH$).XH_2O which is a known renin-inhibiting peptide.
Skellysolve B is as defined in the Merck Index, 10th edition;
t-BDMS is t-butyldimethylsilyl;
TFA is trifluoroacetic acid;
THF is tetrahydrofuran;
TLC is thin layer chromatography;
Tos is p-toluenesulfonyl;
Tr is trityl (triphenylmethyl);
2HPA is (±)-(2-hydroxypropyl)amino; and
UV is ultraviolet.
The wedge-shape line indicates a bond which extends above the plane of the paper relative to the plane of the compound thereon.

The dotted line indicates a bond which extends below the plane of the paper relative to the plane of the compound thereon.

EXPERIMENTAL SECTION

Preparation 1 [1-(Cyclohexylmethyl)-2-[1-[[(1,1-dimethylethyl)-imino]methyl]-2-pyrrolidinyl]-2-hydroxethyl]-carbamic acid, 1,1-dimethylethyl ester, [2R*(1S*,2R*)]-(±) (Formula A-3) and [1-(Cyclohexylmethyl)-2-[1-[[(1,1-

dimethylethyl)imino]methyl]-2-pyrrolidinyl]-2-pyrrobidinyl]-2-pyrrolidinyl-2-hydroxethyl]-carbamic acid, 1,1-dimethylethyl ester, [2R*(1R*,2R*)]-(±) (Formula A-4) Refer to Chart A.

Pyrrolidine formamidine of formula A-2, prepared as described in A.I. Meyers et al., J. Amer. Chem. Soc., 106:3270-3276 (1984), (7.8 g) is added to 100 ml of tetrahydrofuran under nitrogen and subsequently cooled to -80°C (ether/carbon dioxide). Tert-butyl lithium (1.7 m in pentane) is then added dropwise over about 10 minutes. After complete addition, the reaction is warmed to -25°C for 1 hour. The reaction is cooled back to -80°C and the aldehyde of formula A-1 (6.37 g), in tetrahydrofuran (20 ml) is added dropwise over 1 hour. After complete addition, the reaction is stirred an additional 45 minutes at -80°C and then quenched by adding 10 ml of a saturated ammonium chloride solution. The -80°C bath is removed and the reaction is further diluted with 20% sodium hydroxide and extracted with ether. The combined extracts are combined, dried (magnesium sulfate) and solvent removed in vacuo to yield about 10 g of an oily semi-solid. The oily semi-solid is diluted with 25% ethyl acetate/-Skellysolve B and placed in the freezer overnight. 731 mg of the second title product, a white powder, is isolated via filtration. The remaining material is chromatographed over 350 g of silica gel eluting with 2.5% isopropyl amine/ethyl acetate. This column affords 1 g of a very nonpolar compound and the first title product; 2.84 g of a 1/1 mixture of the first and second title products and 1.0 g of a mixture of the second title product and the pyrrolidine formamidine. Chromatography of the first 1.0 g mixture using a 1:1:8 mixture of triethylamine/methanol/ethyl acetate (100 g silica gel) affords 400 mg of the first title product (Formula A-3). Chromatography of the 2.84 g mixture of the first and second title products (Formula A-3 and A-4) yields 1.42 g of the first title product (Formula A-3) and 800 mg of the second title product (Formula A-4). Chromatography of the final 1.0 g mixture affords 200 mg of the second title product (Formula A-4). Yield of the first title product (Formula A-3) is 1.82 g; yield of the second title product (Formula A-4) is 1.73 g.

Physical characteristics are as follows:

First title product:

Oil; IR, cm^{-1}: 3446, 3329, 2967, 2923, 2851, 1712, 1639, 1494, 1449, 1390, 1363, 1171.

^{1}H-NMR (δ, $CDCl_3$): 7.55, 5.04, 3.75, 3.35, 1.95-0.85.

MS at m/e [C.I. ISOB]: 411, 410, 355, 353, 339, 328, 327, 183.

Exact Mass Found: 409.3297.

Second title product:

MP: 89-95°C.

IR, cm^{-1}: 3276, 2950, 2921, 2867, 2854, 1687, 1631, 1527, 1463, 1448, 1374, 1365, 1271, 1180.

^{1}H-NMR (δ, $CDCl_3$): 7.55, 5.12, 3.78-3.31, 2.15-0.75.

MS at m/e [Probe-EI]: 409, 336, 281, 184, 183, 154, 127, 97, 70, 58, 57, 41.

Anal. Found: C, 67.39; H, 11.14; N, 9.85.

Preparation 2 [1-(Cyclohexylmethyl)-2-hydroxy-2-(2-pyrrolidinyl)-ethyl]-[2R*(1R*,2S*)]-carbamic acid (Formula C-2) Refer to Chart C.

The second title product of Preparation 1 (Formula A-4) (710 mg) is added to 5 ml of 95% ethanol. To that solution is added 445 mg of hydrazine, followed by 3.12 mg of acetic acid. That mixture is then heated at 50°C for 1.5 hours. The solvents and excess reagents are removed in vacuo to yield a white solid. Recrystallization from acetonitrile affords 359 mg of the title product.

Physical characteristics are as follows:

MP: 144-5°C.

IR, cm^{-1}: 3351, 2953, 2920, 2868, 2853, 1682, 1536, 1459, 1446, 1377, 1365, 1279, 1174.

MS at m/e: 326, 308, 253, 225, 211, 200, 170, 156, 140, 126, 100, 70.

^{13}C-NMR (DMSO-d_6, PPM): 155.68, 77.46, 74.73, 59.34, 51.00, 45.88, 37.68, 34.10, 33.85, 31.82, 28.34, 28.23, 28.14, 26.20, 25.91, 25.49.

^{1}H-NMR (δ, DMSO-d_6): 6.55, 6.18, 3.50, 3.05, 2.76, 1.90-0.65.

Anal. Found: C, 65.92; H, 10.81; N, 8.55.

Preparation 3 [1-Cyclohexylmethyl)-2-hydroxy-2-(2-pyrrolidinyl)-ethyl]-[2R*(1S*,2S*)]-carbamic acid (Formula B-2) Refer to Chart B.

The first title product of Preparation 1 (Formula A-3) (1.40 g) is added to 5 ml of 95% ethanol. To that solution is added 870 mg of

hydrazine, followed by 6.10 mg of acetic acid. That mixture is then heated at 50°C for 1.5 hours. The solvents and excess reagents are removed in vacuo and the resulting oil diluted with saturated sodium bicarbonate, and extracted with methylene chloride. The methylene chloride is dried (magnesium sulfate) and solvent removed in vacuo to yield a white semi-solid. Crystallization from acetonitrile affords 167 mg of the title product.

Physical characteristics are as follows:

MP: 151-3°C.

IR, cm^{-1}: 3287, 2955, 2916, 2852, 1688, 1463, 1452, 1381, 1378, 1364, 1354, 1345, 1178.

MS at m/e: 326, 308, 253, 225, 211, 201, 170, 155, 140, 126, 100, 70.

^{13}C-NMR (DMSO-d_6, PPM): 155.56, 77.46, 74.91, 60.00, 49.31, 45.75, 33.91, 33.53, 32.39, 28.23, 26.30, 26.15, 25.97, 25.56.

^{1}H-NMR (δ, DMSO-d_6): 6.03, 5.60, 3.58, 2.95, 2.75, 1.9-1.5, 1.4, 1.3-0.7.

Anal. Found: C, 66.18; H, 10.61; N, 8.37.

Preparation 4 2-[3-Cyclohexyl-2-[[(1,1-dimethylethoxy)carbonyl]-amino]-1-hydroxypropyl]-1-pyrrolidine carboxylic acid, phenylmethyl ester[2R*(1R*,2S*)]-(±) (Formula B-3) Refer to Chart B.

The title product of Preparation 3 (10 mg) is added to a saturated solution of aqueous sodium bicarbonate. To that heterogeneous mixture is added 7 μl of benzyloxycarbonyl chloride. The reaction immediately becomes homogeneous and stirring is continued for 30 minutes. The reaction is extracted with methylene chloride. The methylene chloride extracts are dried (magnesium sulfate) and the solvent removed in vacuo. Chromatography (5 g of silica gel, 5-20% ethyl acetate/Skellysolve B) affords 13 mg of the title product.

Physical characteristics are as follows:

IR, cm^{-1}: 3345, 3351, 2975, 2923, 2851, 1710, 1675, 1498, 1449, 1419, 1391, 1364, 1358, 1337, 1171.

^{1}H-NMR (δ, $CDCl_3$): 7.4, 5.59, 5.16, 4.88, 4.05-3.60, 3.50-3.25, 2.20-0.80.

^{13}C-NMR ($CDCl_3$, PPM): 158.8, 155.8, 136.2, 128.6, 128.2, 128.1, 79.0, 77.3, 67.7, 61.8, 49.2, 47.4, 41.0, 34.1, 33.6, 33.2, 28.9, 28.4, 26.6, 26.5, 26.3, 24.3.

Mass spectrum (FAB $[m+1]^+$): Exact Mass Found: 461.3008.

Preparation 5 2-[3-Cyclohexyl-2-[[(1,1-dimethylethoxy)carbonyl]-amino]-1-hydroxypropyl]-1-pyrrolidine carboxylic acid, phenylmethyl ester[2R*(1R*,2R*)]-(±) (Formula C-3) Refer to Chart C.

The title product of Preparation 2 (29 mg) is added to 2 ml of 5% sodium bicarbonate. To that heterogeneous mixture is added 15.2 mg of benzyloxycarbonyl chloride. The solid that fills the flask slowly becomes a viscous oil. After stirring for 30 minutes, the reaction is diluted with methylene chloride. After several extractions with methylene chloride, the organic is dried and solvent removed in vacuo to yield a clear oil. Chromatography over silica gel (7 g) and eluting with 25% ethyl acetate/Skellysolve B affords 35 mg of the title product.

Physical characteristics are as follows:

IR, cm^{-1}: 3354, 2975, 2924, 2851, 1709, 1676, 1677, 1498, 1449, 1419, 1391, 1364, 1359, 1339, 1246, 1172, 1102, 697.

^{1}H-NMR (δ, $CDCl_3$): 7.35, 5.14, 4.99, 3.95-3.50, 3.45-3.25, 2.05-0.61.

^{13}C-NMR ($CDCl_3$, PPM): 158.4, 155.9, 136.2, 128.6, 128.2, 79.0, 78.6, 67.6, 60.8, 50.0, 47.2, 35.4, 34.6, 33.8, 32.5, 28.4, 26.6, 26.4, 26.2, 24.3.

Mass spectrum (FAB $[m+1]^+$): Exact Mass Found: 461.3008.

Preparation 6 2-[3-Cyclohexyl-2-amino-1-hydroxypropyl]-1-pyrrolidine carboxylic acid, phenylmethyl ester,[2R*(1R*,2S*)]-(±) (Formula B-4) Refer to Chart B.

The title product of Preparation 4 (165 mg) is diluted with 2.5 ml of a cold mixture of trifluoroacetic acid/methylene chloride (1:1) cooled to 0°C. After stirring at 0°C for 45 minutes, the reaction is diluted with saturated sodium bicarbonate and the pH adjusted to >10 by adding solid potassium carbonate. The reaction is extracted with methylene chloride, dried (magnesium sulfate) and solvent removed in vacuo to yield 106 mg of the amino alcohol as an oil. This material is used directly in the coupling reaction without further purification.

Preparation 7 2-[3-Cyclohexyl-2-[[2-[[(1,1-dimethylethoxy)carbonyl]-amino]-1-oxo-3-[1-[(phenylmethoxy)methyl]-1H-imidazol-4-yl]propyl]amino]-1-hydroxypropyl]-1-pyrrolidine

carboxylic acid, phenylmethyl ester,[2R*[1R*,2R*-(S*)]]-(±) (Formula B-5) Refer to Chart B.

A mixture of Boc-L-His(πBom)-OH (120 mg), the amine of Preparation 6, (106 mg), diethylphosphorylcyanide (57 mg), and dimethylformamide (3 ml) is cooled to 0°C. To the mixture is added triethylamine (35 μl) dropwise over several minutes. After complete addition, the reaction is stirred at room temperature for 2 hours. The reaction is then diluted with 2/1 ethyl acetate/benzene mixture and washed with saturated sodium bicarbonate, brine and finally water. The organic is dried (magnesium sulfate) and solvent removed in vacuo to yield an oil. Chromatography (50 g silica gel, 5% triethylamine/-ethyl acetate) affords 117 mg of the title product as an oil.

Physical characteristics are as follows:

Mass spectrum (FAB $[m+1]^+$): Exact Mass Found: 718.4186.

^{13}C-NMR: Approximately 2/1 mixture of ll/dl diastereomers.

Preparation 8 N-acetyl-1-formyl-L-tryptophyl-1-prolyl-L-phenylalanyl-N-[1-(cyclohexylmethyl)-2-hydroxy-2-[1-[(phenylmethoxy)carbonyl]-2-pyrrolidinyl)ethyl]-1-[(phenylmethoxy)methyl]-L-histidinamide, [2R-[2R*(1R*,2S*)]]-(Formula B-6) Refer to Chart B.

The title product of Preparation 7 (120 mg) is debocylated by treatment with 30 ml of 50% trifluoroacetic acid/methylene chloride at 0°C twice each for 1 hour. The residue is dissolved in 40 ml of methylene chloride and neutralized with 40 ml of saturated sodium bicarbonate. The aqueous layer is washed 3 times with methylene chloride. The organic layers are combined and dried over magnesium sulfate and the solvent removed under vacuum. The residue is combined with 107 mg of Ac-TrpFor-Pro-Phe-OH and 35 μl of triethylamine and dissolved in 10 ml of anhydrous dimethylformamide. 33 μl of diethylphosphorylcyanide is added to the above mixture at 0°C. After 2 hours, HPLC shows the reaction to be complete. The dimethylformamide is removed under vacuum. The residue is dissolved in 75 ml of ethyl acetate and washed three times with 50 ml of saturated sodium bicarbonate, water, three times with 50 ml of 10% citric acid, water and dried over magnesium sulfate. The crude protected peptide, after lyophilization, gives 100 mg of the title product, which is about 66% pure by reverse-phase HPLC: Using a Synchropak™ C_{18} analytical column (250 mm - 4.6 mm) and a linear gradient (17% B for

2 minutes; 17-100% B over 20 minutes) using solvent A = 10% acetonitrile/water (0.2% trifluoroacetic acid) and solvent B = 70% acetonitrile/water (0.2% trifluoroacetic acid) and a flow rate of 1.5 ml/min.

Example 1 N-Acetyl-1-formyl-L-tryptophyl-1-prolyl-L-phenylalanyl-N-[1-(cyclohexylmethyl)-2-hydroxy-2-(2-pyrrolidinyl)ethyl)-L-histidinamide,[R-R*,S*)]bis(trifluoroacetate) (salt) (Formula B-7) Refer to Chart B.

The crude protected peptide of Preparation 8 (100 mg) is placed in a hydrogen fluoride vessel along with 5 ml of anisole and frozen in liquid nitrogen. Anhydrous hydrogen fluoride (10 ml) is distilled into the vessel and warmed to 0°C. The mixture is then stirred for 1 hour at 0°C. The hydrogen fluoride/anisole is removed under vacuum. The peptide is precipitated with ethyl ether, dissolved in aqueous acetic acid and lyophilized. The crude deprotected peptide gives 40 mg (60% pure by reverse-phase HPLC, k' = 7.2).

Purification:

The peptide is dissolved in 2 ml of dimethylformamide and eluted on a semi-preparative reverse-phase C-18 column (2.2 cm x 27.0 cm) containing Separations Group Vyadac C18. Other conditions include: a linear gradient (0% B for 15 minutes; 0-35% B over 210 minutes; and 35% B for 135 minutes) using solvent A = 10% acetonitrile/water (0.2% trifluoroacetic acid), and solvent B = 70% acetonitrile/water (0.2% trifluoroacetic acid); a flow rate of 2.5 ml/min and collecting 5 ml fractions; and detection at 280 nm (0.5 a.u. full scale). Fractions 161-170 are collected to give 8.8 mg of the title product (93.8% purity).

Physical characteristics are as follows:

Mass spectrum (FAB $[m+H]^+$): m/z of 864.

Preparation 9 2-[3-Cyclohexyl-2-amino-1-hydroxypropyl]-1-pyrrolidine carboxylic acid, phenylmethyl ester,[2R*(1R*,2R*)]-(±) (Formula C-4) Refer to Chart C.

The title product of Preparation 5 (220 mg) is diluted with 2.5 ml of a cold mixture of trifluoroacetic acid/methylene chloride cooled to 0°C. After stirring at 0°C for 45 minutes, the reaction is diluted with saturated sodium bicarbonate and the pH adjusted to >10 by adding solid potassium carbonate. The reaction is extracted with methylene chloride, dried (magnesium sulfate) and solvent removed in

vacuo to yield 144 mg of the title product as an oil. This material is used without further purification in the coupling reaction.

Preparation 10 2-[3-Cyclohexyl-2-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-1-oxo-3-[1-[(phenylmethoxy)methyl]-1H-imidazol-4-yl]propyl]amino]-1-hydroxypropyl]-1-pyrrolidine carboxylic acid, phenylmethyl ester,[2R*-[1R*,2R*(R*)]]-(±) (Formula C-5) Refer to Chart C.

A mixture of Boc-L-His(πBom)-OH (120 mg), the amine of Preparation 9 (107 mg), diethylphosphorylcyanide (57 mg), and dimethylformamide (3 ml) is cooled to 0°C. To that mixture is added triethylamine (35 μl) dropwise over several minutes. After complete addition, the reaction is stirred at room temperature for 2 hours. The reaction is then diluted with a 2/1 mixture of ethyl acetate/benzene and washed with saturated sodium bicarbonate, brine and finally water. The organic is dried (magnesium sulfate) and solvent removed in vacuo to yield an oil. Chromatography (50 g silica gel; 5% triethylamine/ethyl acetate) affords 76 mg of the title product.

Physical characteristics are as follows:

Mass spectrum (FAB $[m+1]^+$): Exact Mass Found: 718.4186.

Preparation 11 N-Acetyl-1-formyl-L-tryptophyl-1-prolyl-L-phenylalanyl-N-[1-(cyclohexylmethyl)-2-hydroxy-2-[1-[(phenylmethoxy)carbonyl]-2-pyrrolidinyl]ethyl]-1-[(phenylmethoxy)methyl]-L-histidinamide[2R-[2R*(1R*,2R*)]]-(Formula C-6) Refer to Chart C.

The title product of Preparation 10 (150 mg) is debocylated by treatment with 30 ml of 50% trifluoroacetic acid/methylene chloride at 0°C twice each for 1 hour. The residue is dissolved in 40 ml of methylene chloride and neutralized with 40 ml of saturated sodium bicarbonate. The aqueous layer is washed 3 times with methylene chloride. The organic layers are combined and dried over magnesium sulfate and the solvent removed under vacuum. The residue is combined with 164 mg of Ac-Trp[For]-Pro-Phe-OH and 60 μl of triethylamine are dissolved in 10 ml of anhydrous dimethylformamide. 51 μl of diethylphosphorylcyanide is added to the 0°C stirring solution. After 2 hours, HPLC shows the reaction to be complete. The dimethylformamide is removed under vacuum. The residue is dissolved in 75 ml of ethyl acetate and washed 3 times with 50 ml of saturated sodium bicarbonate, water, 3 times with 50 ml of 10% citric acid, water and

dried over magnesium sulfate. The crude protected peptide, after lyophilization, gives 180 mg of the title product (containing two peaks: 10% of peak 1 and 38% of peak 2 by reverse-phase HPLC; k'_1 = 12.8, k'_2 = 13, refer to analytical HPLC conditions described in Preparation 8).

Example 2 N-Acetyl-1-formyl-L-tryptophyl-1-prolyl-L-phenylalanyl-N-[1-(cyclohexylmethyl)-2-hydroxy-2-(2-pyrrolidinyl)ethyl]-L-histidinamide-[2S-[2R*(1R*,2S*)]]-bis(trifluoroacetate) (salt) (Formula C-7) and N-Acetyl-1-formyl-L-tryptophyl-1-prolyl-L-phenylalanyl-N-[1-(cyclohexylmethyl)-2-hydroxy-2-(2-pyrrolidinyl)-ethyl]-histidinamide-[2R-[2R*(1R*,2R*)]]-bis(trifluoroacetate) (salt) (Formula C-8) Refer to Chart C.

The crude protected peptide of Preparation 11 (180 mg) is placed in a hydrogen fluoride vessel along with anisole (5 ml) and frozen in liquid nitrogen. Anhydrous hydrogen fluoride (10 ml) is distilled into the vessel and warmed to 0°C. The mixture is then stirred for 1 hour at 0°C. The hydrogen fluoride/anisole is removed under vacuum. The peptide is precipitated with ethyl ether, dissolved in aqueous acetic acid and lyophilized. The crude deprotected peptide gives 100 mg of the two title products (12% of peak one and 33% of peak two by reverse-phase HPLC; k'_1 = 7.2, k'_2 = 7.6).

Purification:

The peptide is dissolved in 2 ml of dimethylformamide and eluted on a semi-preparative reverse phase C-18 column [Separations Group Vyadec C18, 2.2 cm x 27.0 cm Michel-Miller glass column]. Using the following linear gradient: 0% B for 15 minutes; 0-35% B over 210 minutes; and 35% B for 105 minutes [A = 10% acetonitrile/water (0.2% trifluoroacetic acid), B = 70% acetonitrile/water (0.2% trifluoroacetic acid)] with a flow rate of 2.5 ml/min and collecting 5 ml fractions; detection at 280 nm (0.5 a.u. full scale). Fractions 133-142 are collected to give 20 mg of a mixture containing 37% of peak one and 33% of peak two. Fractions 143-150 are collected to give 20 mg of peak two (82% purity by reverse-phase HPLC).

Physical characteristics are as follows:

Mass spectrum (FAB $[m+H]^+$): M/Z of 864 for both title products.

FORMULA CHART

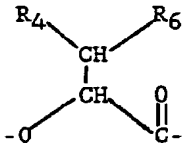
$X\text{-}A_6\text{-}B_7\text{-}C_8\text{-}D_9\text{-}E_{10}\text{-}F_{11}$ I

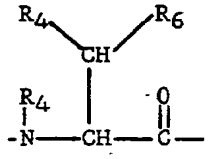
 II

$X\text{-}A_6\text{-}B\text{-}7\text{-}C_8\text{-}OH$ III

$BocNH\text{-}C(R_{90})(R_{91})\text{-}CHO$ V

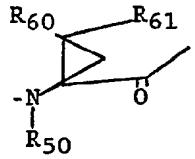
$LiCH_n\text{-}\underset{R_{100}}{\underset{|}{}}\ \underset{R_{101}}{\underset{|}{N(R_{102})}}$ VI

 XL_1

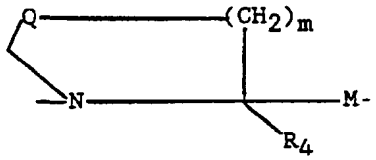
 XL_2

$\underset{|}{\overset{R_{20}}{}}\text{-}N\text{-}CH_2\text{-}C(O)\text{-}$ XL_{2a}

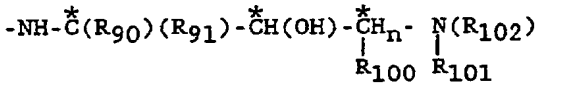
FORMULA CHART (Continued)



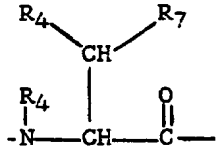
XL_{2b}



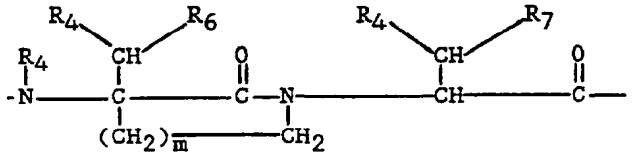
XL_b



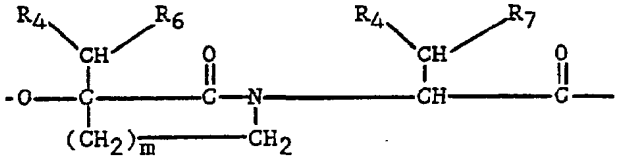
XL_{2c}



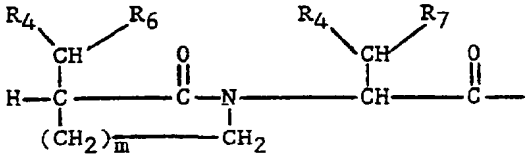
XL_3



XL_7

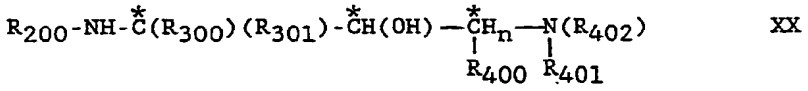


XL_{7a}



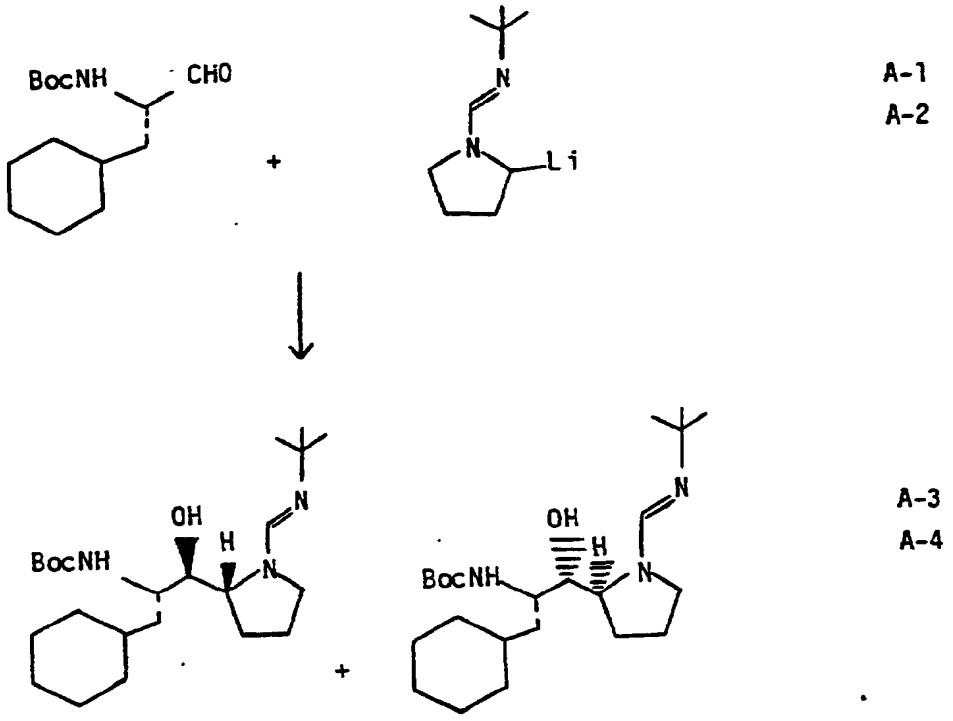
XL_{7b}

FORMULA CHART (Continued)



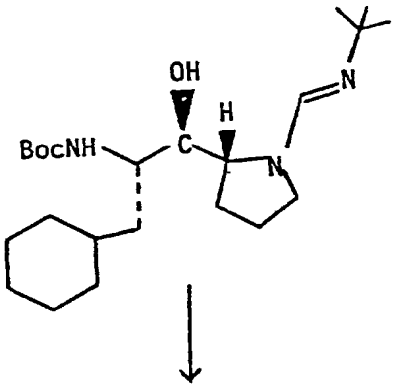
XX

CHART A

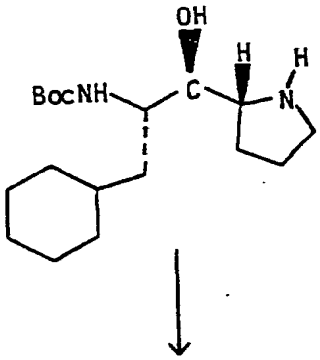


A-1
A-2
A-3
A-4

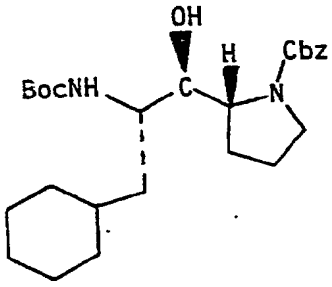
CHART B



B-1 (A-3)

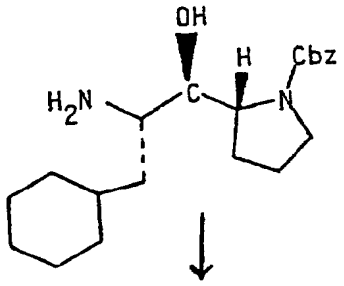


B-2

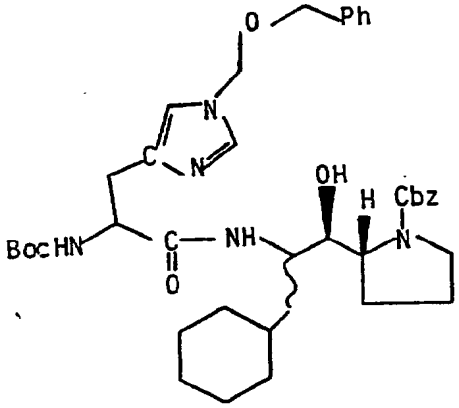


B-3

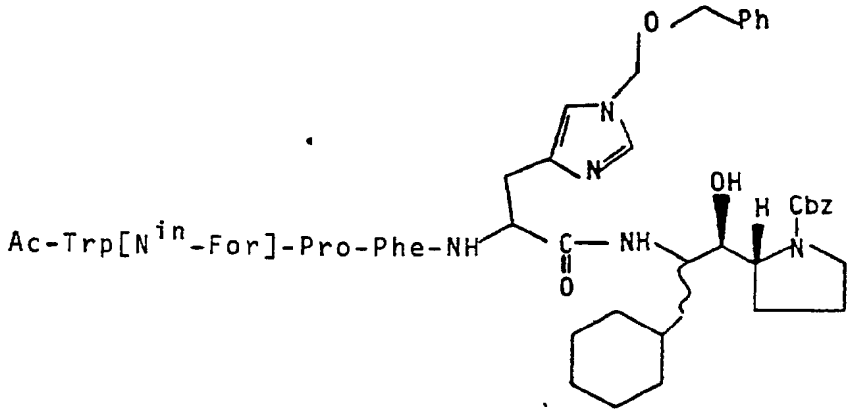
CHART B (Continued)



B-4

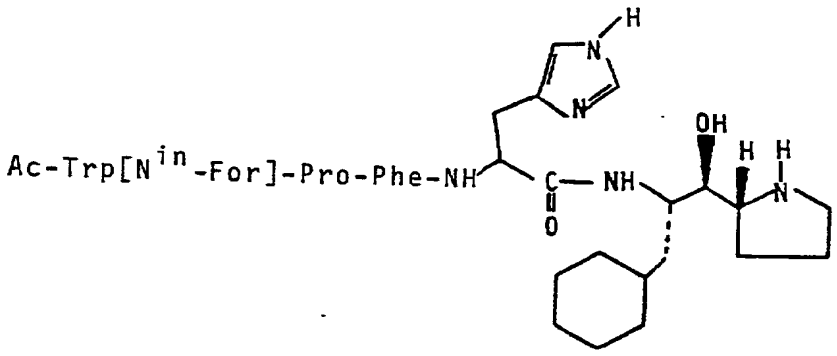


B-5



B-6

CHART B (Continued)



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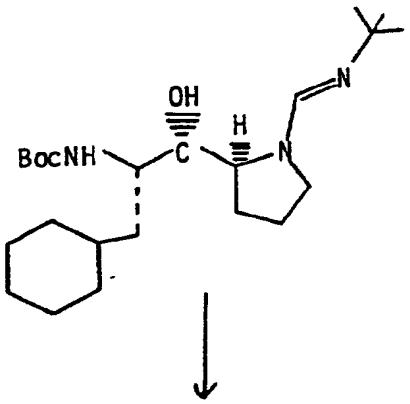
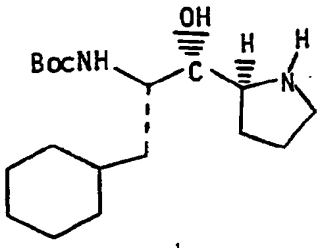
B-7

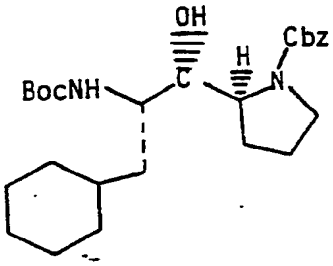
CHART C



C-1 (A-4)

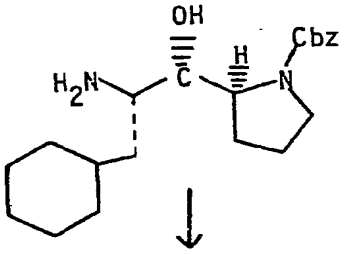


C-2

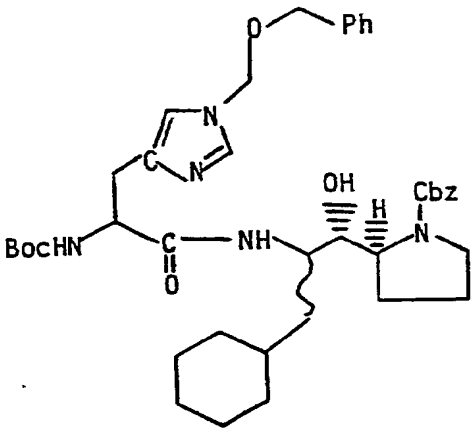


C-3

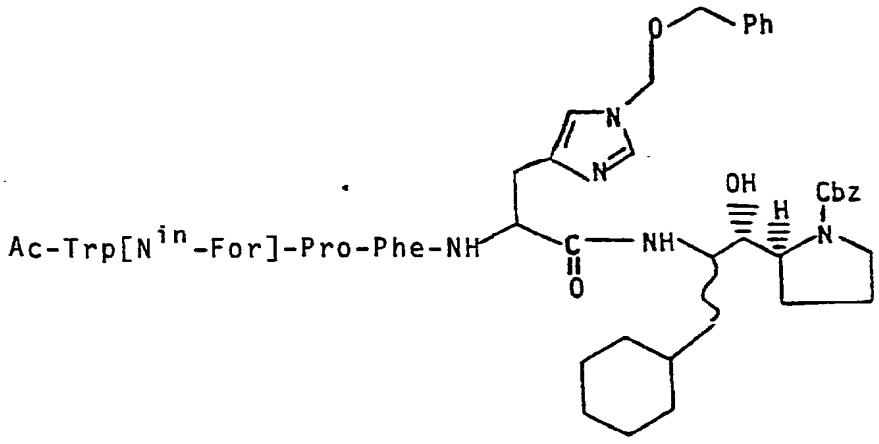
CHART C (Continued)



C-4

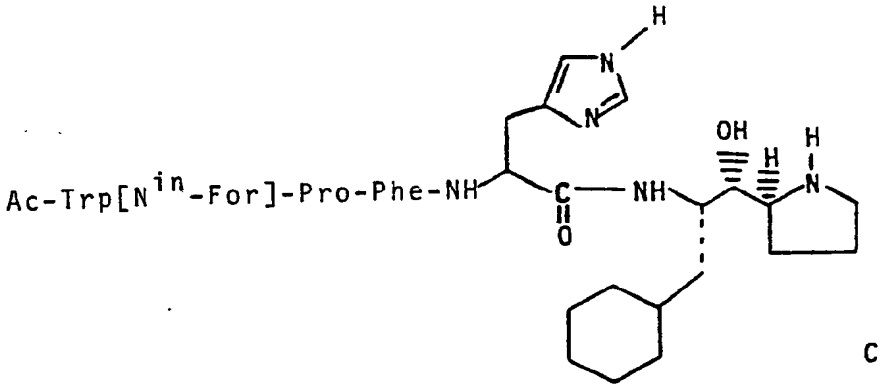


C-5



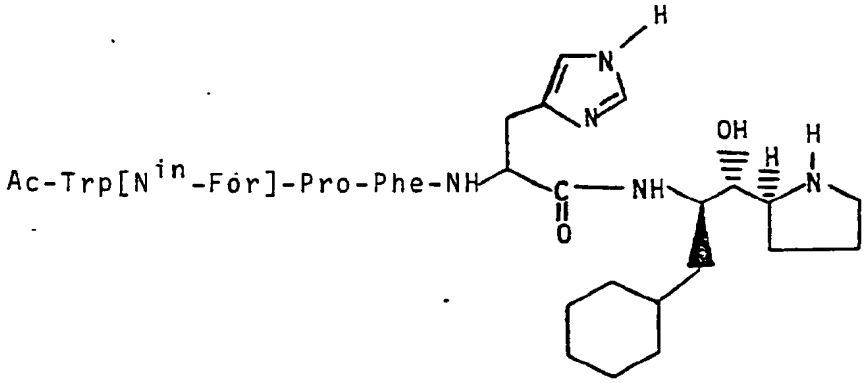
C-6

CHART C (Continued)



C-7

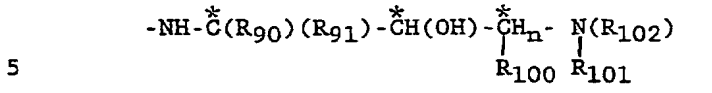
+



C-8

CLAIMS

1. A renin inhibitory peptide having a moiety of the formula XL_{2c}



XL_{2c}

corresponding to the 10,11-position of the renin substrate (angiotensinogen);

wherein * indicates an asymmetric center which is either in the R or S configuration;

wherein R_{90} and R_{91} are the same or different and are:

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p$-C_3-C_7cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_{100} and R_{101} taken together with the carbon atom and the nitrogen atom to which they are bonded to form -Het;

wherein R_{102} is

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p$-C_3-C_7cycloalkyl,

(f) R_5-O-CH_2-C(O)-,

(g) R_5-CH_2-O-C(O)-,

(h) R_5-O-C(O)-,

(i) R_5-$(CH_2)_n$-C(O)-,

(j) R_5-$(CH_2)_n$-C(S)-,

(k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,

(l) R_5-SO_2-$(CH_2)_q$-C(O)-,

(m) R_5-SO_2-$(CH_2)_q$-O-C(O)-,

(n) R_6-$(CH_2)_i$-C(O)-, or

(o) $-[C(O)-AA-NH-]_jX$;

wherein aryl is phenyl or naphthyl substituted by zero to 3 of the following:

(a) C_1-C_3alkyl,

(b) hydroxy,

(c) C_1-C_3alkoxy,
(d) halo,
(e) amino,
(f) mono- or di-C_1-C_3alkylamino,
(g) -CHO,
(h) -COOH,
(i) $COOR_{26}$,
(j) $CONHR_{26}$,
(k) nitro,
(l) mercapto,
(m) C_1-C_3alkylthio,
(n) C_1-C_3alkylsulfinyl,
(o) C_1-C_3alkylsulfonyl,
(p) -N(R_4)-C_1-C_3alkylsulfonyl,
(q) SO_3H,
(r) SO_2NH_2,
(s) -CN, or
(t) $-CH_2NH_2$;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

(i) C_1-C_6alkyl,
(ii) hydroxy,
(iii) trifluoromethyl,
(iv) C_1-C_4alkoxy,
(v) halo,
(vi) aryl,
(vii) aryl C_1-C_4alkyl-,
(viii) amino,
(ix) mono- or di-(C_1-C_4alkyl)amino, and
(x) C_1-C_5alkanoyl;

wherein X is

(a) hydrogen,
(b) C_1-C_7alkyl,
(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,
(e) $-(CH_2)_p$-C_3-C_7cycloalkyl,
(f) R_5-O-CH_2-C(O)-,
(g) R_5-CH_2-O-C(O)-,
(h) R_5-O-C(O)-,
(i) R_5-$(CH_2)_n$-C(O)-,
(j) R_5-$(CH_2)_n$-C(S)-,
(k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,
(l) R_5-SO_2-$(CH_2)_q$-C(O)-,
(m) R_5-SO_2-$(CH_2)_q$-O-C(O)- or
(n) R_6-$(CH_2)_i$-C(O)-;

wherein R_4 at each occurrence is the same or different and is
(a) hydrogen,
(b) C_1-C_5alkyl,
(c) $-(CH_2)_p$-aryl,
(d) $-(CH_2)_p$-Het,
(e) $-(CH_2)_p$-C_3-C_7 cycloalkyl, or
(f) 1- or 2-adamantyl;

wherein R_5 is
(a) C_1-C_6alkyl,
(b) C_3-C_7cycloalkyl,
(c) aryl,
(d) -Het, or
(e) 5-oxo-2-pyrrolidinyl;

wherein R_6 is
(a) hydrogen,
(b) C_1-C_5alkyl,
(c) $-(CH_2)_p$-aryl,
(d) $-(CH_2)_p$-Het,
(e) $-(CH_2)_p$-C_3-C_7cycloalkyl, or
(f) 1- or 2-adamantyl;

wherein R_{26} is
(a) hydrogen,
(b) C_1-C_3alkyl, or
(c) phenyl-C_1-C_3alkyl;

wherein i is zero to five, inclusive;

wherein j is one to three, inclusive;

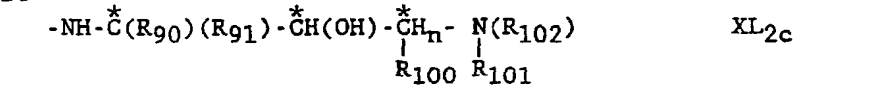
wherein for each occurrence n is independently an integer of

zero to five, inclusive;

wherein p is zero to two, inclusive;

wherein q is one to five, inclusive.

2. In a renin inhibitory peptide, the improvement which comprises inclusion in the renin inhibitory peptide of a moiety of the formula XL_{2c}



XL_{2c}

corresponding to the 10,11-position of the renin substrate (angiotensinogen);

wherein * indicates an asymmetric center which is either in the R or S configuration;

wherein R_{90} and R_{91} are the same or different and are:

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p$-C_3-C_7cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_{100} and R_{101} taken together with the carbon atom and the nitrogen atom to which they are bonded to form -Het;

wherein R_{102} is

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p$-C_3-C_7cycloalkyl,

(f) R_5-O-CH_2-C(O)-,

(g) R_5-CH_2-O-C(O)-,

(h) R_5-O-C(O)-,

(i) R_5-$(CH_2)_n$-C(O)-,

(j) R_5-$(CH_2)_n$-C(S)-,

(k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,

(l) R_5-SO_2-$(CH_2)_q$-C(O)-,

(m) R_5-SO_2-$(CH_2)_q$-O-C(O)-,

(n) R_6-$(CH_2)_i$-C(O)-, or

(o) $-[C(O)-AA-NH-]_jX$;

wherein aryl is phenyl or naphthyl substituted by zero to three of the following:

(a) C_1-C_3alkyl,
(b) hydroxy,
(c) C_1-C_3alkoxy,
(d) halo,
(e) amino,
(f) mono- or di-C_1-C_3alkylamino,
(g) -CHO,
(h) -COOH,
(i) $COOR_{26}$,
(j) $CONHR_{26}$,
(k) nitro,
(l) mercapto,
(m) C_1-C_3alkylthio,
(n) C_1-C_3alkylsulfinyl,
(o) C_1-C_3alkylsulfonyl,
(p) -N(R_4)-C_1-C_3alkylsulfonyl,
(q) SO_3H,
(r) SO_2NH_2,
(s) -CN, or
(t) $-CH_2NH_2$;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to three of the following:

(i) C_1-C_6alkyl,
(ii) hydroxy,
(iii) trifluoromethyl,
(iv) C_1-C_4alkoxy,
(v) halo,
(vi) aryl,
(vii) aryl C_1-C_4alkyl-,
(viii) amino,
(ix) mono- or di-(C_1-C_4alkyl)amino, and
(x) C_1-C_5alkanoyl;

wherein X is

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het,

(e) -$(CH_2)_p$-C_3-C_7cycloalkyl,

(f) R_5-O-CH_2-C(O)-,

(g) R_5-CH_2-O-C(O)-,

(h) R_5-O-C(O)-,

(i) R_5-$(CH_2)_n$-C(O)-,

(j) R_5-$(CH_2)_n$-C(S)-,

(k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,

(l) R_5-SO_2-$(CH_2)_q$-C(O)-,

(m) R_5-SO_2-$(CH_2)_q$-O-C(O)- or

(n) R_6-$(CH_2)_i$-C(O)-;

wherein R_4 at each occurrence is the same or different and is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het,

(e) -$(CH_2)_p$-C_3-C_7 cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_5 is

(a) C_1-C_6alkyl,

(b) C_3-C_7cycloalkyl,

(c) aryl,

(d) -Het, or

(e) 5-oxo-2-pyrrolidinyl;

wherein R_6 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het,

(e) -$(CH_2)_p$-C_3-C_7cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_{26} is

(a) hydrogen,

(b) C_1-C_3alkyl, or

(c) phenyl-C_1-C_3alkyl;

wherein i is zero to five, inclusive;

wherein j is one to three, inclusive;

wherein for each occurrence n is independently an integer of zero to five, inclusive;

wherein p is zero to two, inclusive;

wherein q is one to five, inclusive.

3. The renin inhibitory peptide of claim 1 wherein, in the moiety of the formula XL_{2c}, R_{102} is

(a) hydrogen,

(b) $-(CH_2)_p$-Het,

(c) R_5-O-CH_2-C(O)-,

(d) R_5-O-C(O)-, or

(e) R_6-$(CH_2)_i$-C(O)-.

4. The renin inhibitory peptide of claim 2 wherein, in the moiety of the formula XL_{2c}, R_{102} is

(a) hydrogen,

(b) $-(CH_2)_p$-Het,

(c) R_5-O-CH_2-C(O)-,

(d) R_5-O-C(O)-, or

(e) R_6-$(CH_2)_i$-C(O)-.

5. The renin inhibitory peptide of claim 1 of the formula I

$$X\text{-}A_6\text{-}B_7\text{-}C_8\text{-}D_9\text{-}E_{10}\text{-}F_{11} \qquad I$$

wherein X is

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p$-C_3-C_7cycloalkyl,

(f) R_5-O-CH_2-C(O)-,

(g) R_5-CH_2-O-C(O)-,

(h) R_5-O-C(O)-,

(i) R_5-$(CH_2)_n$-C(O)-,

(j) R_5-$(CH_2)_n$-C(S)-,

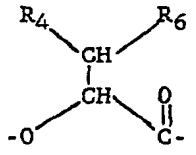
(k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,

(l) R_5-SO_2-$(CH_2)_q$-C(O)-,

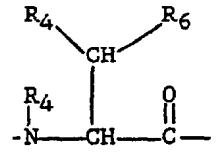
(m) R_5-SO_2-$(CH_2)_q$-O-C(O)- or

(n) R_6-$(CH_2)_i$-C(O)-;

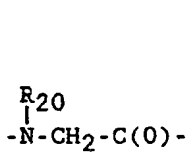
wherein A_6 is absent or a divalent moiety of the formula XL_1, XL_2, XL_{2a} or XL_{2b};



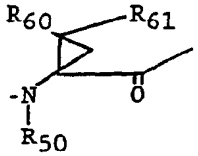
XL_1



XL_2

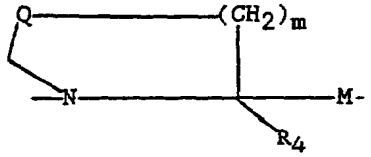


XL_{2a}



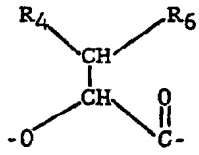
XL_{2b}

wherein B_7 is absent or a divalent moiety of the formula XL_b;

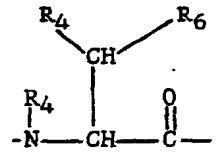


XL_b

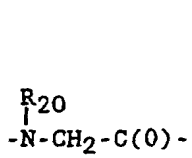
wherein C_8 is absent or a divalent moiety of the formula XL_1, XL_2, XL_{2a} or XL_{2b};



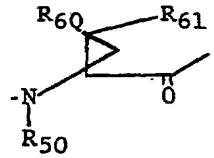
XL_1



XL_2

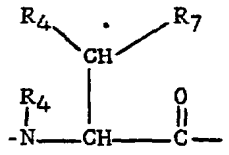


XL_{2a}

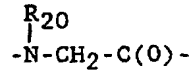


XL_{2b}

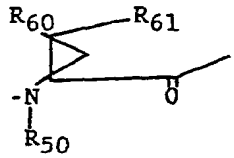
wherein D_9 is absent or a divalent moiety of the formula XL_3, XL_{2a} or XL_{2b};



XL_3

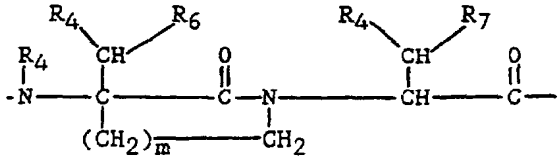


XL_{2a}

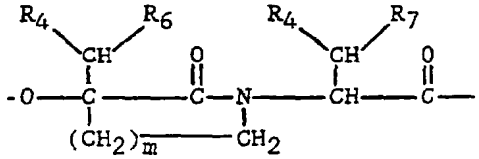


XL_{2b}

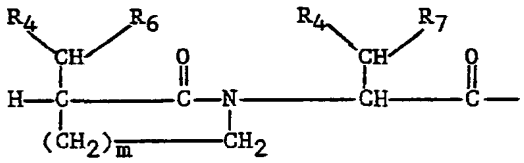
or wherein C_8-D_9 is XL_7, XL_{7a}, or when X, A_6 and B_7 are absent, XL_{7b};



XL_7

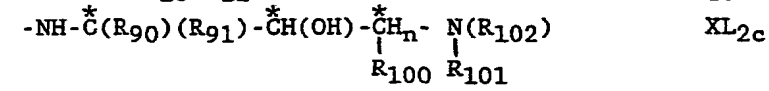


XL_{7a}



XL_{7b}

wherein E_{10}-F_{11} is a moiety of the formula XL_{2c};



XL_{2c}

wherein * indicates an asymmetric center which is either in the R or S configuration;

wherein Z is

(a) $-O-R_{10}$,

(b) $-N(R_4)R_{14}$, or

(c) C_4-C_8cyclic amino;

wherein R is

(a) isopropyl,

(b) isobutyl,

(c) phenylmethyl, or

(d) C_3-C_7cycloalkyl;

wherein R_1 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) aryl,

(d) C_3-C_7cycloalkyl,

(e) -Het,

(f) C_1-C_3alkoxy, or

(g) C_1-C_3alkylthio;

wherein R_2 is

(a) hydrogen, or

(b) $-CH(R_3)R_4$;

wherein R_3 is

(a) hydrogen,

(b) hydroxy,

(c) C_1-C_5alkyl,

(d) C_3-C_7cycloalkyl,

(e) aryl,

(f) -Het,

(g) C_1-C_3alkoxy, or

(h) C_1-C_3alkylthio;

wherein R_4 at each occurrence is the same or different and is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het,

(e) -$(CH_2)_p$-C_3-C_7cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_5 is

(a) C_1-C_6alkyl,

(b) C_3-C_7cycloalkyl,

(c) aryl,

(d) -Het, or

(e) 5-oxo-2-pyrrolidinyl;

wherein R_6 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het,

(e) -$(CH_2)_p$-C_3-C_7cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_7 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) hydroxy,

(d) amino C_1-C_4alkyl-,

(e) guanidinyl C_1-C_3alkyl-,

(f) aryl,

(g) -Het,

(h) methylthio,

(i) -$(CH_2)_p$-C_3-C_7cycloalkyl, or

(j) amino;

wherein R_8 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) hydroxy,

(d) aryl,

(e) -Het,

(f) guanidinyl C_1-C_3alkyl-, or

(g) -$(CH_2)_p$-C_3-C_7cycloalkyl;

wherein R_9 is

(a) hydrogen,

(b) hydroxy,

(c) amino C_1-C_4alkyl-, or

(d) guanidinyl C_1-C_3alkyl-;

wherein R_{10} is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) -$(CH_2)_n R_{16}$,

(d) -$(CH_2)_n R_{17}$,

(e) C_3-C_7cycloalkyl,

(f) a pharmaceutically acceptable cation,

(g) -$CH(R_{25})$-CH_2-R_{15}, or

(h) -CH_2-$CH(R_{12})$-R_{15};

wherein R_{11} is -R or -R_2;

wherein R_{12} is -$(CH_2)_n$-R_{13};

wherein R_{13} is

(a) aryl,

(b) amino,

(c) mono-, di or tri-C_1-C_3alkylamino,

(d) -Het,

(e) C_1-C_5alkyl

(f) C_3-C_7cycloalkyl,

(g) C_2-C_5alkenyl,

(h) C_3-C_7cycloalkenyl,

(i) hydroxy,

(j) C_1-C_3alkoxy,

(k) C_1-C_3alkanoyloxy,

(l) mercapto,

(m) C_1-C_3alkylthio,

(n) -COOH,

(o) -CO-O-C_1-C_6alkyl,

(p) -CO-O-CH_2-(C_1-C_3alkyl)-N(C_1-C_3alkyl)$_2$,

(q) -CO-$NR_{22}R_{26}$;

(r) C_4-C_7cyclic amino,

(s) C_4-C_7cycloalkylamino,

(t) guanidyl,

(u) cyano,

(v) N-cyanoguanidyl,

(w) cyanoamino,

(x) (hydroxy C_2-C_4alkyl)amino, or

(y) di-(hydroxyC_2-C_4alkyl)amino;

wherein R_{14} is

(a) hydrogen,

(b) C_1-C_{10}alkyl,

(c) $-(CH_2)_n-R_{18}$,

(d) $-(CH_2)_n-R_{19}$,

(e) $-CH(R_{25})-CH_2-R_{15}$,

(f) $-CH_2-CH(R_{12})-R_{15}$,

(g) (hydroxy C_1-C_8alkyl), or

(h) (C_1-C_3alkoxy)C_1-C_8alkyl;

wherein R_{15} is

(a) hydroxy,

(b) C_3-C_7cycloalkyl,

(c) aryl,

(d) amino,

(e) mono-, di-, or tri- C_1-C_3alkylamino,

(f) mono- or di-(hydroxy C_2-C_4alkyl)amino,

(g) -Het,

(h) C_1-C_3alkoxy-,

(i) C_1-C_3alkanoyloxy-,

(j) mercapto,

(k) C_1-C_3alkylthio-,

(l) C_1-C_5alkyl,

(m) C_4-C_7cyclic amino,

(n) C_4-C_7cycloalkylamino,

(o) C_1-C_5alkenyloxy,

(p) C_3-C_7cycloalkenyl;

wherein R_{16} is

(a) aryl,

(b) amino,

(c) mono- or di- (C_1-C_3alkyl)amino,

(d) hydroxy,

(e) C_3-C_7cycloalkyl,

(f) C_4-C_7cyclic amino, or

(g) C_1-C_3alkanoyloxy;

wherein R_{17} is

(a) -Het,

(b) C_1-C_5alkenyl,

(c) C_3-C_7cycloalkenyl,

(d) C_1-C_3alkoxy,

(e) mercapto,

(f) C_1-C_3alkylthio,

(g) -COOH,

(h) -CO-O-C_1-C_6alkyl,

(i) -CO-O-CH_2-(C_1-C_3alkyl)-N(C_1-C_3alkyl)$_2$,

(j) -CO-$NR_{22}R_{26}$,

(k) tri-C_1-C_3alkylamino,

(l) guanidyl,

(m) cyano,

(n) N-cyanoguanidyl,

(o) (hydroxy C_2-C_4alkyl)amino,

(p) di-(hydroxy C_2-C_4alkyl)amino, or

(q) cyanoamino;

wherein R_{18} is

(a) amino,

(b) mono-, or di- (C_1-C_3alkyl)amino,

(c) C_4-C_7cyclic amino; or

(d) C_4-C_7cycloalkylamino;

wherein R_{19} is

(a) aryl,

(b) -Het,

(c) tri-C_1-C_3alkylamino,

(d) C_3-C_7cycloalkyl,

(e) C_1-C_5alkenyl,

(f) C_3-C_7cycloalkenyl,

(g) hydroxy,

(h) C_1-C_3alkoxy,

(i) C_1-C_3alkanoyloxy,

(j) mercapto,

(k) C_1-C_3alkylthio,

(l) -COOH,

(m) -CO-O-C_1-C_6alkyl,

(n) -CO-O-CH_2-(C_1-C_3alkyl)-N(C_1-C_3alkyl)$_2$,

(o) -CO-$NR_{22}R_{26}$,

(p) guanidyl,

(q) cyano,

(r) N-cyanoguanidyl,

(s) cyanoamino,

(t) (hydroxy C_2-C_4alkyl)amino,

(u) di-(hydroxy C_2-C_4alkyl)amino; or

(v) -SO_3H;

wherein R_{20} is

(a) hydrogen,

(b) C_1-C_5alkyl, or

(c) aryl-C_1-C_5alkyl;

wherein R_{21} is

(a) -NH_2, or

(b) -OH;

wherein R_{22} is

(a) hydrogen, or

(b) C_1-C_3alkyl;

wherein R_{23} is

(a) -$(CH_2)_n$-OH,

(b) -$(CH_2)_n$-NH_2,

(c) aryl, or

(d) C_1-C_3alkyl;

wherein R_{24} is

(a) -R_1,

(b) -$(CH_2)_n$-OH, or

(c) -$(CH_2)_n$-NH_2;

wherein R_{25} is

(a) hydrogen,

(b) C_1-C_3alkyl, or

(c) phenyl-C_1-C_3alkyl;

wherein R_{26} is

(a) hydrogen,

(b) C_1-C_3alkyl, or

(c) phenyl-C_1-C_3alkyl;

wherein R_{50} is

(a) hydrogen,
(b) C_1-C_5alkyl,
(c) -$(CH_2)_p$-aryl,
(d) -$(CH_2)_p$-Het,
(e) -$(CH_2)_p$-C_3-C_7cycloalkyl, or
(f) 1- or 2-adamantyl;

wherein R_{60} and R_{61} are the same or different and are

(a) hydrogen,
(b) C_1-C_5alkyl,
(c) -$(CH_2)_p$-aryl,
(d) -$(CH_2)_p$-Het,
(e) -$(CH_2)_p$-C_3-C_7cycloalkyl, or
(f) 1- or 2-adamantyl;

or wherein R_{60} and R_{61} taken together form a spirocycle of the formula II

II

wherein R_{70} is

(a) -CHR_{80},
(b) -O-,
(c) -S-,
(d) -SO-,
(e) -SO_2-, or
(f) -NR_{81};

wherein R_{80} and R_{81} are the same or different and are

(a) hydrogen,
(b) C_1-C_5alkyl,
(c) -$(CH_2)_p$-aryl,
(d) -$(CH_2)_p$-Het,
(e) -$(CH_2)_p$-C_3-C_7cycloalkyl, or
(f) 1- or 2-adamantyl;

wherein R_{90} and R_{91} are the same or different and are:

(a) hydrogen,
(b) C_1-C_7alkyl,
(c) -$(CH_2)_p$-aryl,
(d) -$(CH_2)_p$-Het,
(e) -$(CH_2)_p$-C_3-C_7cycloalkyl, or
(f) 1- or 2-adamantyl;

wherein R_{100} and R_{101} taken together with the carbon atom and the nitrogen atom to which they are bonded to form -Het;

wherein R_{102} is

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p$-C_3-C_7cycloalkyl,

(f) R_5-O-CH_2-C(O)-,

(g) R_5-CH_2-O-C(O)-,

(h) R_5-O-C(O)-,

(i) R_5-$(CH_2)_n$-C(O)-,

(j) R_5-$(CH_2)_n$-C(S)-,

(k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,

(l) R_5-SO_2-$(CH_2)_q$-C(O)-,

(m) R_5-SO_2-$(CH_2)_q$-O-C(O)-,

(n) R_6-$(CH_2)_i$-C(O)-, or

(o) $-[C(O)-AA-NH-]_jX$;

wherein i is zero to five, inclusive;

wherein j is one to three, inclusive;

wherein m is one or two;

wherein for each occurrence n is independently an integer of zero to five, inclusive;

wherein p is zero to two, inclusive;

wherein q is one to five, inclusive;

wherein Q is

(a) $-CH_2-$,

(b) -CH(OH)-,

(c) -O-, or

(d) -S-; and

wherein M is

(a) -CO-, or

(b) $-CH_2-$;

wherein aryl is phenyl or naphthyl substituted by zero to three of the following:

(a) C_1-C_3alkyl,

(b) hydroxy,

(c) C_1-C_3alkoxy,

(d) halo,
(e) amino,
(f) mono- or di-C_1-C_3alkylamino,
(g) -CHO,
(h) -COOH,
(i) $COOR_{26}$,
(j) $CONHR_{26}$,
(k) nitro,
(l) mercapto,
(m) C_1-C_3alkylthio,
(n) C_1-C_3alkylsulfinyl,
(o) C_1-C_3alkylsulfonyl,
(p) -N(R_4)-C_1-C_3alkylsulfonyl,
(q) SO_3H,
(r) SO_2NH_2,
(s) -CN, or
(t) $-CH_2NH_2$;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to three of the following:

(i) C_1-C_6alkyl,
(ii) hydroxy,
(iii) trifluoromethyl,
(iv) C_1-C_4alkoxy,
(v) halo,
(vi) aryl,
(vii) aryl C_1-C_4alkyl-,
(viii) amino,
(ix) mono- or di-(C_1-C_4alkyl)amino, and
(x) C_1-C_5alkanoyl;

with the overall provisos that:

(1) R_{18} or R_{19} is hydroxy, mercapto, or amino, or a mono-substituted nitrogen containing group bonded through the nitrogen only when n is not one;

(2) R_{12} is $-(CH_2)_n-R_{13}$ and n is zero and both R_{13} and R_{15} are

oxygen-, nitrogen-, or sulfur-containing substituents bonded through the hetero atom, only when the hetero atom is not also bonded to hydrogen;

(3) R_{17} or R_{19} is -COOH only when n for that moiety is other than zero;

(4) R_{16} or R_{17} is an amino-containing substituent, hydroxy, mercapto, or -Het bonded through the hetero atom only when n for that substituent is an integer from two to five, inclusive;

(5) when R_{12} is $-(CH_2)_n-R_{13}$ and n is zero, then R_{13} and R_{15} cannot both be -COOH; and

(6) R_{17} or R_{19} is -Het, only when -Het is other than cyclic amino;

or a carboxy-, amino-, or other reactive group-protected form thereof;

or a pharmaceutically acceptable acid addition salt thereof.

6. The renin inhibitory peptide of claim 5 wherein -Het is

(a) azetidinyl,
(b) pyrrolidinyl,
(c) piperidyl,
(d) 4-aryl-piperidyl,
(e) piperidino,
(f) thiazolyl,
(g) thiazenyl,
(h) piperazinyl,
(i) morpholinyl,
(j) morpholino,
(k) pyrrolinyl,
(l) 3-hydroxy-methylene-pyrrolinyl,
(m) pyrrolyl,
(n) indolyl, or
(o) 1,2,3,4-tetrahydro-isoquinolyl.

7. The renin inhibitory peptide of claim 6 wherein X is R_5-O-C(O)-; wherein A_6 is XL_2; wherein B_7 is XL_b;

wherein C_8 is XL_2;

wherein D_9 is XL_3;

wherein E_{10}-F_{11} is XL_{2c};

wherein R_{90} is hydrogen;

wherein R_{91} is methylcyclohexyl;

wherein R_{100} and R_{101} taken together with the carbon atom and the nitrogen atom to which they are bonded to form 2-pyrrolidinyl;

wherein R_{102} is hydrogen.

8. The renin inhibitory peptide of claim 7 wherein E_{10}-F_{11} is (1-cyclohexylmethyl-1-amino-2-hydroxy-2-(2-pyrrolidinyl))ethyl.

9. N-Acetyl-1-formyl-L-tryptophyl-1-prolyl-L-phenylalanyl-N-[1-(cyclohexylmethyl)-2-hydroxy-2-(2-pyrrolidinyl)ethyl]-L-histidinamide-[2S-[2R*(1R*,2S*)]]-bis(trifluoroacetate) (salt), a compound of claim 8.

10. N-Acetyl-1-formyl-L-tryptophyl-1-prolyl-L-phenylalanyl-N-[1-(cyclohexylmethyl)-2-hydroxy-2-(2-pyrrolidinyl)ethyl]-histidinamide-[2R-[2R*(1R*,2R*)]]-bis(trifluoroacetate) (salt), a compound of claim 8.

11. N-Acetyl-1-formyl-L-tryptophyl-1-prolyl-L-phenylalanyl-N-[1-(cyclohexylmethyl)-2-hydroxy-2-(2-pyrrolidinyl)ethyl)-L-histidinamide,[R-R*,S*)]bis(trifluoroacetate) (salt), a compound of claim 8.

12. A peptide of the formula III

X-A_6-B_7-C_8-OH III

wherein X is

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het,

(e) -$(CH_2)_p$-C_3-C_7cycloalkyl,

(f) R_5-O-CH_2-C(O)-,

(g) R_5-CH_2-O-C(O)-,

(h) R_5-O-C(O)-,

(i) R_5-$(CH_2)_n$-C(O)-,

(j) $R_5-(CH_2)_n-C(S)-$,

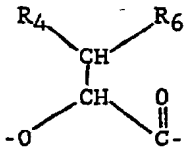
(k) $R_4N(R_4)-(CH_2)_n-C(O)-$,

(l) $R_5-SO_2-(CH_2)_q-C(O)-$,

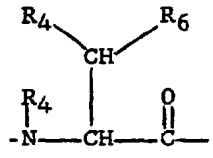
(m) $R_5-SO_2-(CH_2)_q-O-C(O)-$ or

(n) $R_6-(CH_2)_i-C(O)-$;

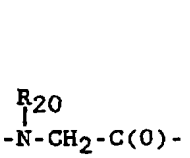
wherein A_6 is absent or a divalent moiety of the formula XL_1, XL_2, XL_{2a} or XL_{2b};



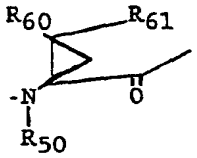
XL_1



XL_2

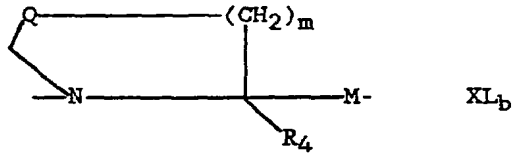


XL_{2a}



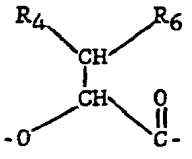
XL_{2b}

wherein B_7 is absent or a divalent moiety of the formula XL_b;

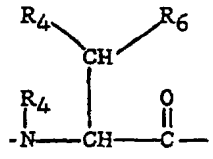


XL_b

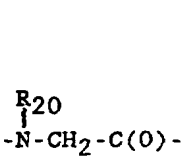
wherein C_8 is absent or a divalent moiety of the formula XL_1, XL_2, XL_{2a} or XL_{2b};



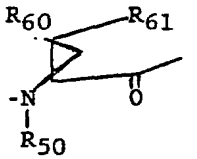
XL_1



XL_2



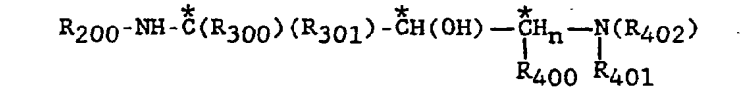
XL_{2a}



XL_{2b}.

13. Ac-Trp[N^{in}-For]-Pro-Phe-OH, a compound of claim 12.

14. A compound of the formula XX



XX

wherein * indicates an asymmetric center which is either in the R or S configuration;

wherein R_{200} is

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p-C_3-C_7$cycloalkyl,

(f) R_5-O-CH_2-C(O)-,
(g) R_5-CH_2-O-C(O)-,
(h) R_5-O-C(O)-,
(i) R_5-$(CH_2)_n$-C(O)-,
(j) R_5-$(CH_2)_n$-C(S)-,
(k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,
(l) R_5-SO_2-$(CH_2)_q$-C(O)-,
(m) R_5-SO_2-$(CH_2)_q$-O-C(O)-, or
(n) R_6-$(CH_2)_i$-C(O)-;

wherein R_{300} and R_{301} are the same or different and are:
(a) hydrogen,
(b) C_1-C_7alkyl,
(c) -$(CH_2)_p$-aryl,
(d) -$(CH_2)_p$-Het,
(e) -$(CH_2)_p$-C_3-C_7cycloalkyl, or
(f) 1- or 2-adamantyl;

wherein R_{400} and R_{401} taken together with the carbon atom and the nitrogen atom to which they are bonded to form -Het;

wherein R_{402} is
(a) hydrogen,
(b) C_1-C_7alkyl,
(c) -$(CH_2)_p$-aryl,
(d) -$(CH_2)_p$-Het,
(e) -$(CH_2)_p$-C_3-C_7cycloalkyl,
(f) R_5-O-CH_2-C(O)-,
(g) R_5-CH_2-O-C(O)-,
(h) R_5-O-C(O)-,
(i) R_5-$(CH_2)_n$-C(O)-,
(j) R_5-$(CH_2)_n$-C(S)-,
(k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,
(l) R_5-SO_2-$(CH_2)_q$-C(O)-,
(m) R_5-SO_2-$(CH_2)_q$-O-C(O)-,
(n) R_6-$(CH_2)_i$-C(O)-,
(o) -$[C(O)$-AA-NH-$]_j X_1$, or
(p) -C=N-C_1-C_7alkyl;

wherein aryl is phenyl or naphthyl substituted by zero to 3 of the following:
(a) C_1-C_3alkyl,

(b) hydroxy,
(c) C_1-C_3alkoxy,
(d) halo,
(e) amino,
(f) mono- or di-C_1-C_3alkylamino,
(g) -CHO,
(h) -COOH,
(i) $COOR_{26}$,
(j) $CONHR_{26}$,
(k) nitro,
(l) mercapto,
(m) C_1-C_3alkylthio,
(n) C_1-C_3alkylsulfinyl,
(o) C_1-C_3alkylsulfonyl,
(p) -N(R_4)-C_1-C_3alkylsulfonyl,
(q) SO_3H,
(r) SO_2NH_2,
(s) -CN, or
(t) $-CH_2NH_2$;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

(i) C_1-C_6alkyl,
(ii) hydroxy,
(iii) trifluoromethyl,
(iv) C_1-C_4alkoxy,
(v) halo,
(vi) aryl,
(vii) aryl C_1-C_4alkyl-,
(viii) amino,
(ix) mono- or di-(C_1-C_4alkyl)amino, and
(x) C_1-C_5alkanoyl;

wherein X is

(a) hydrogen,
(b) C_1-C_7alkyl,

(c) $-(CH_2)_p$-aryl,
(d) $-(CH_2)_p$-Het,
(e) $-(CH_2)_p$-C_3-C_7cycloalkyl,
(f) R_5-O-CH_2-C(O)-,
(g) R_5-CH_2-O-C(O)-,
(h) R_5-O-C(O)-,
(i) R_5-$(CH_2)_n$-C(O)-,
(j) R_5-$(CH_2)_n$-C(S)-,
(k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,
(l) R_5-SO_2-$(CH_2)_q$-C(O)-,
(m) R_5-SO_2-$(CH_2)_q$-O-C(O)- or
(n) R_6-$(CH_2)_i$-C(O)-;

wherein R_4 at each occurrence is the same or different and is
(a) hydrogen,
(b) C_1-C_5alkyl,
(c) $-(CH_2)_p$-aryl,
(d) $-(CH_2)_p$-Het,
(e) $-(CH_2)_p$-C_3-C_7 cycloalkyl, or
(f) 1- or 2-adamantyl;

wherein R_5 is
(a) C_1-C_6alkyl,
(b) C_3-C_7cycloalkyl,
(c) aryl,
(d) -Het, or
(e) 5-oxo-2-pyrrolidinyl;

wherein R_6 is
(a) hydrogen,
(b) C_1-C_5alkyl,
(c) $-(CH_2)_p$-aryl,
(d) $-(CH_2)_p$-Het,
(e) $-(CH_2)_p$-C_3-C_7cycloalkyl, or
(f) 1- or 2-adamantyl;

wherein R_{26} is
(a) hydrogen,
(b) C_1-C_3alkyl, or
(c) phenyl-C_1-C_3alkyl;

wherein i is zero to five, inclusive;

wherein j is one to three, inclusive;

wherein for each occurrence n is independently an integer of zero to five, inclusive;

wherein p is zero to two, inclusive;

wherein q is one to five, inclusive.

15. A compound of claim 14

wherein R_{200} is

(a) hydrogen,

(b) $-(CH_2)_p$-Het,

(c) R_5-O-CH_2-C(O)-,

(d) R_5-O-C(O)-,

(e) R_6-$(CH_2)_i$-C(O)-, or

(f) R_5-CH_2-O-C(O)-;

wherein R_{300} is hydrogen;

wherein R_{301} is

(a) C_1-C_7alkyl,

(b) $-(CH_2)_p$-aryl,

(c) $-(CH_2)_p$-Het, or

(d) $-(CH_2)_p$-C_3-C_7cycloalkyl;

wherein R_{400} and R_{401} taken together with the carbon atom and the nitrogen atom to which they are bonded to form -Het;

wherein R_{402} is

(a) hydrogen,

(b) $-(CH_2)_p$-Het,

(c) R_5-O-CH_2-C(O)-,

(d) R_5-O-C(O)-, or

(e) R_6-$(CH_2)_i$-C(O)-,

(f) R_5-CH_2-O-C(O)-, or

(g) -C=N-C_1-C_7alkyl.

16. A compound of claim 15

wherein R_{200} is hydrogen, benzyloxycarbonyl, or t-butyloxycarbonyl;

wherein R_{300} is hydrogen;

wherein R_{301} is methylcyclohexyl;

wherein R_{400} and R_{401} taken together with the carbon atom and the nitrogen atom to which they are bonded to form 2-pyrrolidinyl;

wherein R_{402} is hydrogen, benzyloxycarbonyl, t-butyloxycarbonyl

or -C=N-(1,1-dimethylethyl).

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 88/03274

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 K 5/04; C 07 K 7/04; C 07 K 5/02; C 07 K 7/02; A 61 K 37/64

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	C 07 K; A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A, 0231919 (SQUIBB) 12 August 1987 see pages 118-123; claim 1 --	1-16
A	EP, A, 0173481 (UPJOHN) 5 March 1986	

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16th February 1989	16. 03. 89
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	P.C.G. VAN DER PUTTEN

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers ....., because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. Claims: 9-11,13 completely; 1-8,12,14-16 partially. The compounds of claims 9-11 and intermediates for their production.
2. Claims: 1-8,12,14-16 partially. Compounds not covered by subject 1.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

   9-11, 13 completely and 1-8,12,14-16 partially

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 8803274 SA 24641

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 07/03/89
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0231919	12-08-87	AU-A- 6815387	06-08-87
		JP-A- 62258365	10-11-87
EP-A- 0173481	05-03-86	JP-A- 61063641	01-04-86